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Food Allergy Genetics and Epigenetics: A Review of Genome-Wide Association Studies

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ABSTRACT

In this review, we provide an overview of food allergy genetics and epigenetics aimed at clinicians and researchers. This includes a brief review of the current understanding of genetic and epigenetic mechanisms, inheritance of food allergy, as well as a discussion of advantages and limitations of the different types of studies in genetic research. We specifically focus on the results of genome-wide association studies in food allergy, which have identified 16 genetic variants that reach genome-wide significance, many of which overlap with other allergic diseases, including asthma, atopic dermatitis, and allergic rhinitis. Identified genes for food allergy are mainly involved in epithelial barrier function (e.g., *FLG*, *SERPINB7*) and immune function (e.g., *HLA*, *IL4*). Epigenome-wide significant findings at 32 loci are also summarized as well as 14 additional loci with significance at a false discovery of $<1\times10^{-4}$. Integration of epigenetic and genetic data is discussed in the context of disease mechanisms, many of which are shared with other allergic diseases. The potential utility of genetic and epigenetic discoveries is deliberated. In the future, genetic and epigenetic markers may offer ways to predict the presence or absence of clinical IgE-mediated food allergy among sensitized individuals, likelihood of development of natural tolerance, and response to immunotherapy.

Immunoglobulin-E-mediated food allergy (FA) is an improper immune response to food allergens. Symptoms vary from mild reactions to anaphylaxis, and FA is associated with decreased quality of life [1]. Atopic diseases are often co-expressed, including FA, atopic dermatitis (AD), asthma, eosinophilic esophagitis (EoE), and allergic rhinitis (AR) [2, 3]. Prevalence of FA varies, reflecting differences in populations, diet, and environment [1]. Heritability estimates and concordance rates for

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FA traits from twin studies vary (51%–82%), but are higher in monozygous compared to dizygous twins (Table 1) [4–7]. There is strong aggregation of FA within families [8] and population-based studies show a family history of allergic disease modestly increases the risk of FA in the offspring (odds ratio (OR) 1.4 for one family member; OR 1.8 for ≥ two family members with allergic disease) [2]. These observations have motivated researchers to identify genetic and epigenetic factors of FA, which is thought to be a complex polygenic disorder with low penetrance rather than a Mendelian disorder. However, the role of rare variants has not been studied outside of primary immunodeficiency disorders that have FA as part of their clinical phenotype (Table S1). Key concepts in genetics and epigenetics are provided in Figure 1 [9–11].

1 | Genetic Risk Factors for Food Allergy and Their Relationship With Other Atopic Diseases

Many loci for FA have been identified through large-scale genetic studies, candidate gene studies, family studies, and investigation of rare (< 5%) [12] monogenic disorders that feature FA as a primary clinical feature; each study type has advantages and disadvantages (Table 2) [11–18]. High throughput genome-wide association studies (GWAS) can be powerful tools for identifying variant-trait associations and for the discovery of new biological mechanisms through an unbiased survey of the genome. However, these may be limited in the identification of rare variants and common variants not captured in the chip design [14], and direct causal links cannot be made due to linkage disequilibrium (i.e., nonrandom association of alleles at different loci) [18]. Many tests for association are conducted, necessitating correction for multiple testing. Large samples sizes are therefore needed to achieve statistical significance, which can make rigorous diagnosis of food allergic cases by oral food challenge (OFC) less feasible. Many studies rely on self-report or doctor's diagnosis in order to accrue these samples [19], which may lead to misclassification and reduction of power. Replication of GWAS findings are crucial to provide convincing statistical evidence for association, and to rule out association due to artifact [20]. Candidate gene studies involve the selection of a specific gene or genes to investigate a priori based on current knowledge, and may have higher power, particularly in founder populations, but may miss genetic factors that are yet unidentified in association with the disease, meaning that novel pathways and genes may be overlooked [11]. GWAS are often referred to as hypothesis-generating studies, while candidate gene studies are sometimes considered confirmatory studies. Family studies may have higher statistical power to discover genes, as there is generally a more homogeneous phenotype and probably a more limited set of contributing genes and pathways, but this relies on the ability to find willing participants with the appropriate phenotype; this design has been combined with genome-wide approaches [15, 20]. Animal studies of FA allow for more environmental controls, genetic manipulation, and specific environmental interventions, but no animal model completely

TABLE 1 | Estimation of the heritability of food allergy from twin studies.

Twin pairs	Median age (range)	Diagnostic criteria	Concordance rate	Heritability estimation	Reference
14 MZ 44 DZ	5 years (1–58 years)	Clinical history AND peanut sIgE (level n/r)	64.3% (peanut allergy MZ) 6.8% (peanut allergy DZ)	81.6% (peanut allergy)	Sicherer [5]
34 MZ 46 DZ	4.8 years (0.59–35.8 years)	At least one twin with allergist-diagnosed food allergy, AND convincing history AND positive SPT/sIgE/food challenge	59% (peanut allergy MZ) 29% (peanut allergy DZ)	—	Kivisto [6]
			55% (pistachio allergy MZ) 0% (pistachio allergy DZ)		
1315 (# MZ/DZ not listed)	NR	Parental report of "food allergy ever"	78% (MZ) 40% (DZ)	—	Ullemar [4]
472 MZ 354 DZ	17.5 (12–28 years)	No clinical history Positive SPT to cow milk, egg white, soybean, wheat, peanut, walnut, fish mix, shellfish mix, sesame seed (MultiTest II)	53% (peanut sensitization MZ) 29% (peanut sensitization DZ)	51% (peanut sensitization)	Liu [7]
			58% (shellfish MZ) 45% (shellfish DZ)	68% (shellfish sensitization)	

Abbreviations: DZ, dizygotic; MZ, monozygotic; n/r, not reported; sIgE, specific IgE; SPT, skin prick test.

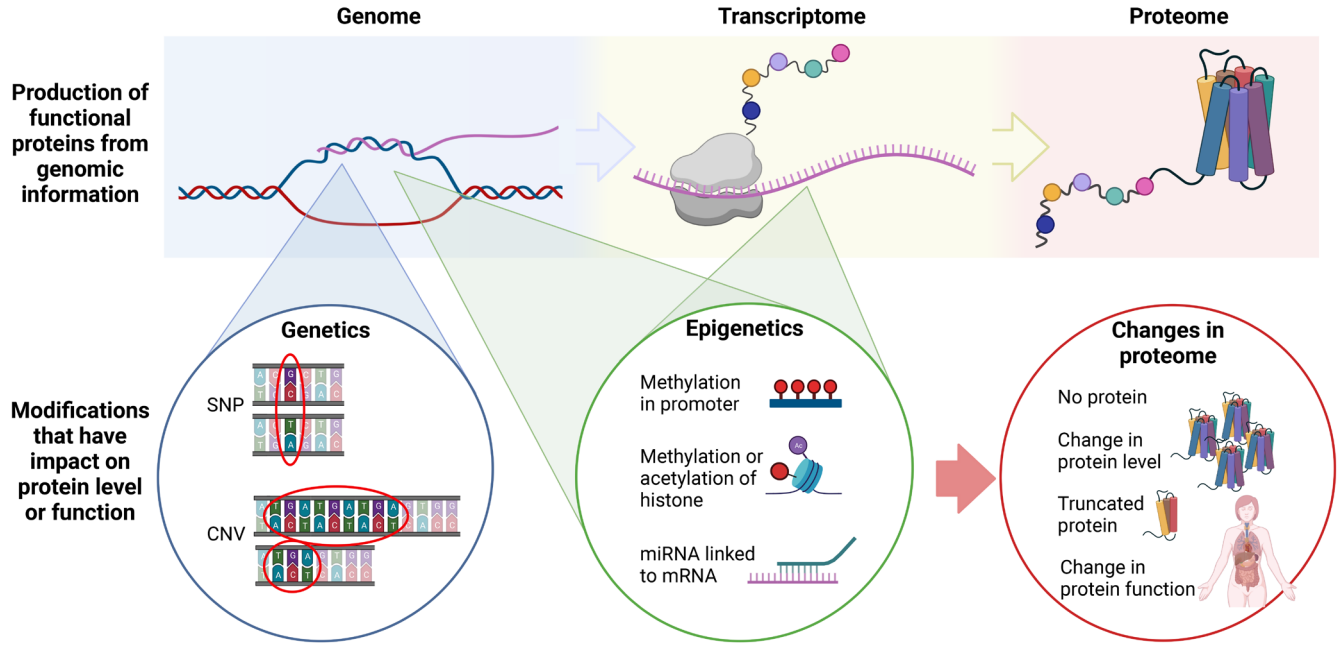

FIGURE 1 | Review of genetic and epigenetic mechanisms. Double-stranded DNA makes up the genome and is coiled to make chromatin fibers and then wrapped around histones to make chromosomes. Genomic changes called single nucleotide polymorphisms (SNP) are a one base-pair change in germline DNA. These can occur both in exons (protein coding) and introns (non-coding regions, which often have regulatory function). Changes in DNA that involve a change in repetition of sections of the genome are known as copy number variants (CNV). DNA must be accessible in order to be transcribed into messenger RNAs (mRNA), which constitute the transcriptome. mRNA are then translated into proteins which collectively make up the proteome. Epigenetic mechanisms—shaped by external factors—include DNA methylation, histone modification and non-coding RNA. Long non-coding and micro RNAs (miRNA; short single strands of RNA) can bind to transcribed mRNA affecting translation. Genetic and epigenetic modifications can impact protein expression, including a complete lack of protein production, a change in protein levels, or a change in protein sequence that leads to a truncated protein or a protein with impaired function. This figure has been created with BioRender.com.

recapitulates the human pathology of FA [16]. In this review, we will focus on statistically-significant genetic risk loci for FA found in a genome-wide approach, as identified through the Open Targets Genetics resource (last updated October 2022), and cross-verified with PubMed searches and the GWAS catalog September 2024 (Table 3) [21]. Currently, these primarily fall within two major groupings—immune and epithelial barrier function.

To date, 16 loci have been associated with clinically diagnosed FA at genome-wide significance ($p < 5 \times 10^{-8}$) with 10 of these shared with other atopic diseases suggesting a common genetic etiology (Table 3) [28–30]. These single nucleotide polymorphisms (SNPs) are identified by their position on a chromosome and their reference SNP cluster ID (rs) number. Filaggrin (*FLG*) loss-of-function (LoF) mutations at Chromosome (Chr) 1q and variants on Chr11q13.5 [29, 31] are significantly associated with FA, AD, asthma, and AR [32–36]. *FLG* encodes a skin barrier protein, and its role in multiple atopic diseases is discussed further below. The Chr11q13.5 region has additionally been identified as a risk locus for EoE [37, 38]. It contains 2 genes, leucin rich repeat containing 32 (*LRRC32*), which tethers transforming growth factor beta (TGFB) to the surface of FOXP3^{+} regulatory T-cells (Tregs) [39], and the histone-modification protein *EMSY* (encoded by the *c11orf30 gene*) [40]. *EMSY* polymorphisms are a risk factor for asthma in the Chinese Han population [41]. Similarly, two other loci, one located in the cytokine gene cluster on Chr5q31 near *IL4*, and one on Chr18 in *SERPINB7* are also associated with multiple allergic diseases [30, 42–45]. Additional loci shared between FA and asthma are found in the human leukocyte antigen (*HLA*) region [46]. The *SERPINB* cluster initially identified by a GWAS on FA was also associated with early onset of allergic diseases [30, 47]. Thus, there is considerable genetic overlap of FA genetic variants with asthma, AD, AR, EoE, and early onset of allergic diseases; the identified genes for FA are discussed in further detail below.

2 | Genetic Loci Related to Epithelial Barrier Function in Food Allergy

FLG LoF mutations result in complete lack of protein expression of filaggrin, a skin barrier protein. *FLG* mutations are associated with early onset, severity, and persistence of AD [48]. *FLG* mutations were detected with similar cumulative allele frequencies (~5%–5.5%) in groups of different genetic ancestries but exhibit population-specific mutation patterns [49]. An association between *FLG* and FA was found in both GWAS and candidate gene studies [50, 51], first identified for peanut allergy (PA) [51], but now with similar risk estimates for multiple types of FA [49]. *FLG* mutations were associated with the persistence of hen's egg and cow's milk allergy [49] and severe FA in AD [52].

High levels of environmental exposure to peanut allergen are associated with increased risk of PA in individuals with known *FLG* LoF mutations [53, 54], which may suggest the skin acts as the route of sensitization in FLG-deficient children. While *FLG* LoF mutations were not genotyped on any of the commercial

TABLE 2 | Advantages and disadvantages of types of genetic studies for food allergy.

Study type	Advantages	Disadvantages
Genome-wide association study	• Powerful when performed in large study populations • Unbiased by a priori selection of genes • Can identify new biological mechanisms and novel pathways • "Hypothesis-generating" study	• Initially more costly, but now more affordable • Larger sample size needed • Phenotype may be what is available if samples taken from larger cohort study • Initially limited in identification of rare variants; higher density chips and imputation now used • Variants depend on chip design/coverage • Direct causal links difficult to establish due to linkage disequilibrium • Chips may lack ethnic diversity in the design, which may result in loss of power when used on admixed populations
Candidate gene studies	• "Confirmatory" study • Less complication by surrounding SNPs in LD	• Selection of gene(s) to investigate a priori based on current knowledge; may miss unidentified genetic factors
Family studies	• Less confounding due to more controlled genetic and non-genetic factors • Higher statistical power to discover genes for monogenic/oligogenic traits • Can be combined with genome-wide approach	• Requires sufficient families with affected members to be recruited
Monogenic Mendelian disorders that feature food allergy as a primary presenting clinical feature	• High penetrance of genetic effects aids in interpretation of pathophysiology • 23% of genes that are linked to highly penetrant Mendelian disease are associated with at least one complex disorder; may help to identify pathways within complex common diseases • May show systemic relevance of a gene or protein	• Specific mutation in Mendelian disorder is unlikely to be carried by individuals with common complex diseases • Phenotype may be rare
Animal studies	• Precise control over genetic and environmental factors • Intervention at different time points possible • Genetic manipulation possible	• No animal model completely recapitulates human disease

References: Musunuru et al., Chakravarti, Carter et al., Tam et al., Kanzi et al., Schulke et al., Spataro et al., Uffelmann et al. [11–18].

GWAS arrays, rs12123821 in the 1.9 Mb region containing the epidermal differentiation complex on Chr1q21 exhibited genome-wide significance for FA [22]; this area contains multiple genes involved in regulation and function of the skin barrier [55]. A conditional analysis revealed that this association was due to the two most common *FLG* mutations. However, a residual association was still detectable between *FLG* and the repetin gene (*RPTN*), suggesting additional genetic risk factors in this region, which is unsurprising as the epidermal differentiation complex contains over 50 genes that direct the development and regulation of the skin [56]. *FLG* also contains an intragenic copy number variant (CNV) due to its repeated FLG motif, which encodes the portion that becomes natural moisturizing factor [57]; low copy number is correlated with increased risk of AD and chemical penetration through the skin barrier [58], but has not yet been evaluated in FA.

Additional risk loci for FA have been identified in or near genes with epithelial barrier function, including an intronic variant in the *SERPINB* cluster on Chr18q22 [22]. Although most other serpins are protease inhibitors that circulate in the bloodstream, clade B serpins are intracellular and may protect cells from proteolysis [59]. The associated FA gene, serpin family B member 7 (*SERPINB7*) is implicated in Nagashima-type autosomal recessive palmoplantar keratosis, a disease with a skin barrier defect [60]. An intergenic locus near *SERPINB2*, also known as plasminogen activator inhibitor-2 (*PAI2*), has also been identified in egg allergy [22]. PAI2 is a serine protease inhibitor involved in apoptosis, cell differentiation, and the innate immune response [61]. Leukocyte expression of *SERPINB10*, which inhibits apoptosis of allergenic T-cells in asthma [62], is correlated to GWAS variants in the *SERPINB7* and *SERPINB2* genes in the cluster described above [22].

Other novel loci identified may also be epithelial barrier-related. An intergenic variant near integrin alpha 6 gene (*ITGA6*), involved in barrier function [63], reached genome-wide significance for PA but remains to be replicated in independent data sets [23]. The other flanking gene for this locus, *DLX2*, is a homeobox protein with roles in placental formation and neural crest migration [64]. Three SNPs in an intergenic region between two genes on Chr11 (*EMSY*, *LRRC32*) have been identified

TABLE 3 | Genome-wide significant variants associated with clinically diagnosed food allergy (significant at p-values $\leq 5\times10^{-8}$).

Variants associated with food allergy at genome-wide significance										
SNP ID (variants associated at genome-wide significance)	**Chr**	**Position**	**Flanking coding genes Nearest gene transcription start site in bold**	**Location**	**Non-coding genes between flanking coding genes Those overlapping lead variant in bold**	***p***	**Study population**	**Diagnostic Criteria**	**Reference**	**Other associated traits[b]**
rs12123821 (1_152206676_C_T)	1	152206676	*RPTN-**HRNR***	Intergenic	***FLG-AS1 RP11-107M16.2***	2.6×10^{-15}	**(I)** 523 German children and 2682 population-based adult controls	**(I) Food allergy** OFC	Marenholz [22]	Asthma, atopic dermatitis, allergic rhinitis
rs115218289 (2_172401022_C_A)	2	172401022	*DLX2-**ITGA6***	Intergenic	*DLX2-DT AC104088.1 RP11-744C22.2 RP11-744C22.1 AC078883.4*	1.80×10^{-8}	**(II)** Canadian peanut allergy genome-wide association study: 850 cases, self-identified Caucasian, 926 Australian self-identified hyper-control subjects Meta-analysis food allergy: 7267 cases, 29, 084 controls Meta-analysis peanut allergy: 1582 cases, 5446 controls Canadian, American, Australian, German and Dutch cases	**(II) Peanut allergy** (1) Clinical history[e] AND specific IgE ≥ 0.35 kU/L AND SPT (≥ 3 mm) (2) Clinical history AND SPT (≥ 3 mm) (3) Clinical history AND specific IgE ≥ 0.35 kU/L (4) Uncertain history[f] AND specific IgE ≥ 15 kU/L AND SPT (≥ 3 mm) (5) No history of reaction[g] AND specific IgE ≥ 15 kU/L AND SPT (≥ 3 mm)	Asai [23]	—
rs188127752 (3_731841_G_T)	3	731841	*CHL1-**CNTN6***	Intergenic	***LINC01266***	1.2×10^{-9}	UKBiobank	Allergy or anaphylactic reaction to food[d]	UKB Neale v2, https://www.nealelab.is/uk-biobank [24]	—
rs11949166 (5_132691989_A_T)	5	132691989	***IL4**-KIF3A*	Intergenic	***AC004237.1***	4.3×10^{-17}	See entry **(I)**	See entry **(I)**	Marenholz [22]	Asthma, atopic dermatitis, eosinophil counts

(Continues)

TABLE 3 | (Continued)

Variants associated with food allergy at genome-wide significance										
SNP ID (variants associated at genome-wide significance)	**Chr**	**Position**	**Flanking coding genes Nearest gene transcription start site in bold**	**Location**	**Non-coding genes between flanking coding genes Those overlapping lead variant in bold**	***p***	**Study population**	**Diagnostic Criteria**	**Reference**	**Other associated traits[b]**
rs7192 (6_32443869_T_G)	6	32443869	***HLA-DRA***	Exonic (missense variant)	—	2.7×10^{-9}	**(III)** American, European ancestry: 2197 subjects (1049 children; 1148 parents) Non-European Ancestry: 497 subjects (234 children; 263 parents)	**(III) Peanut allergy** (1) convincing history[e] of clinical allergic reaction upon ingestion (2) detectable food-specific IgE ($\geq$0.10 kU L^{-1}) and/or positive SPT (wheal n/r)	Hong [25]	Asthma, eosinophil count
rs9271588 (6_32623176_T_C)	6	32623176	*HLA-DRB1-* ***HLA-DQA1***	Intergenic	—	1.11×10^{-26}	**(IV)** 452 Japanese females, 2700 female Pharma SNP Consortium Japanese population controls Mean age: cases 48.2 (12.6), controls 57.9 (13.3)	**(IV) Hydrolysed wheat protein allergy** (HWP) allergy[c] (1) use of soap containing HWP; (2) allergic symptoms within several to 30 min after using the soap, allergic symptoms after eating wheat products, or both; or (3) a positive laboratory test result, SPT, and/or basophil activation test result	Noguchi [26]	Asthma, eosinophil count, lung function (FEV_1/FVC)
rs9273440 (6_32659784_T_C)	6	32659784	***HLA-DQB1***	3′UTR Variant upstream	—	1.7×10^{-11}	See entry **(I)**	**Food allergy** See entry **(I)**	Marenholz [22]	Asthma, eosinophil count, lung function (FVC) forced expiratory volume in 1-s (FEV_1)

(Continues)

TABLE 3 | (Continued)

Variants associated with food allergy at genome-wide significance										
SNP ID (variants associated at genome-wide significance)	**Chr**	**Position**	**Flanking coding genes Nearest gene transcription start site in bold**	**Location**	**Non-coding genes between flanking coding genes Those overlapping lead variant in bold**	***p***	**Study population**	**Diagnostic Criteria**	**Reference**	**Other associated traits[b]**
rs9275596 (6_32713854_C_T)	6	32713854	*HLA-DQB1-* ***HLA-DQA2***	Intergenic	*XXbac-BPG254F23.7*	6.3×10^{-11}	See entry **(III)**	**Peanut allergy** See entry **(III)**	Hong [25]	Asthma, eosinophil count, predicted forced expiratory volume in 1-s (FEV_1), lung function (FEV_1/FVC)
rs9277630 (6_33114490_C_A)	6	33114490	***HLA-DPA1***- *COL11A2*	Intergenic	*HCG24*	1.36×10^{-11}	**(V) Discovery Set:** Japanes cases $n=77$, median age 51 (42–63); Pharma SNP consortium controls $n=924$, median age 36 (29–46) **Replication Set:** Japanese cases $n=91$, median age 44 (36–54); Japan Biological Informatics Consortium controls $n=435$, median age 37 (29–47)	**(V) Wheat allergy** (1) occurrence of immediate-type allergic reactions, such as urticaria, after taking wheat products owing to secondary factors, including exercise, non-steroidal anti-inflammatory drugs and/or alcohol consumption; (2) induction of immediate-type allergic reactions by oral wheat provocation test [3] detection of wheat protein (including ≥0.70 kUa/L to ω-5 gliadin)-specific IgE in serum; and (4) positive SPT (wheal n/r)	Fukunaga [27]	Eosinophil counts
rs2212434[a] (11_76570549_C_T)	11	76570549	*EMSY-* ***LRRC32***	Intergenic	*LINC02757 RP11-672A2.6 RP11-672A2.4 AP001189.4*	9.2×10^{-11}	See entry **(I)**	**Food allergy** See entry **(I)**	Marenholz [22]	Allergic rhinitis, allergy, hypersensitivity, or anaphylaxis, asthma, atopic dermatitis, eosinophil count

(Continues)

TABLE 3 | (Continued)

Variants associated with food allergy at genome-wide significance										
SNP ID (variants associated at genome-wide significance)	**Chr**	**Position**	**Flanking coding genes Nearest gene transcription start site in bold**	**Location**	**Non-coding genes between flanking coding genes Those overlapping lead variant in bold**	***p***	**Study population**	**Diagnostic Criteria**	**Reference**	**Other associated traits[b]**
rs7936070[a] (11_76582483_G_T)	11	76582483	*EMSY-**LRRC32***	Intergenic	*LINC02757 RP11-672A2.6 RP11-672A2.4 AP001189.4*	5.86×10^{-11}	See entry **(II)**	**Food allergy**[c] See entry **(II)**	Asai [23]	Allergic rhinitis, allergic sensitization, allergy, hypersensitivity, or anaphylaxis, asthma, atopic dermatitis, atopic march, self-reported allergy, eosinophil count, IgE levels, IgE grass sensitization
rs7936434[a] (11_76582761_G_C)	11	76582761	*EMSY-**LRRC32***	Intergenic	*LINC02757 RP11-672A2.6 RP11-672A2.4 AP001189.4*	7.50×10^{-11}	See entry **(II)**	**Food allergy** See entry **(II)**	Asai [23]	Allergic rhinitis, allergy, hypersensitivity, or anaphylaxis, asthma, atopic dermatitis, eosinophil count, IgE grass sensitization, IgE levels, allergic sensitization, self-reported allergy, atopic march
rs59325236 (16_7706047_G_A)	16	7706047	***RBFOX1***	Intronic	—	1.31×10^{-8}	See entry **(IV)**	**Wheat allergy** See entry **(IV)**	Noguchi [26]	—
rs12964116 (18_63775385_A_G)	18	63775385	*SERPINB7*	Intronic	—	1.8×10^{-8}	See entry **(I)**	**Food allergy** See entry **(I)**	Marenholz [22]	Asthma, allergic rhinitis, atopic dermatitis

(Continues)

TABLE 3 | (Continued)

Variants associated with food allergy at genome-wide significance										
SNP ID (variants associated at genome-wide significance)	**Chr**	**Position**	**Flanking coding genes Nearest gene transcription start site in bold**	**Location**	**Non-coding genes between flanking coding genes Those overlapping lead variant in bold**	***p***	**Study population**	**Diagnostic Criteria**	**Reference**	**Other associated traits[b]**
rs1243064 (18_63846741_T_A)	18	63846741	***SERPINB2***	Intergenic	—	4.2×10^{-8}	See entry above **(I)**	**Egg allergy** See entry **(I)**	Marenholz [22]	—
rs523865 (20_914238_A_G)	20	914238	*ANGPT4*	Intronic	—	4.09×10^{-8}	See entry **(II)**	**Food allergy** See entry **(II)**	Asai [23]	—

Notes: All data was extracted from Open Targets Genetics (October 2022; https://genetics.opentargets.org/) (PMCID: PMC7778936), an open-access integrative resource that aggregates human GWAS results and allows exploration of variant-gene-trait associations from UK Biobank, FinnGen, and the GWAS Catalog. Further inspection in PubMed and the GWAS Catalog as of September 2024 was conducted. Variant name indicates the genome location from the *Homo sapiens* Genome Reference Consortium Human Build 38 (GRCh38); for example, for 6_32713854_C_T, the chromosome is 6, the location is 32713854, and reference allele is C, while the alternative (effect) allele is T.
Abbreviations: FEV_1/FVC, forced expiratory volume in 1 s/forced vital capacity; PMID, PubMed publication identification number.
[a]rs7936434, rs7936070, rs2212434 variants within *EMSY-LRRC32* locus are in high LD (LD > 0.8) [21].
[b]Curated list of additional allergy-related comorbidities and clinical biomarkers associated at genome-wide significance with the variant of interest.
[c]Includes self-reported food allergy phenotypes.
[d]Through ICD9 and ICD10 physician and diagnostic coding.
[e]Convincing history includes: two mild symptoms or signs, **OR** one moderate or one severe symptom or sign, **AND** occurring within 120 min after known peanut contact or ingestion.
[f]Uncertain history includes: one mild symptom or sign occurring within 120 min after known peanut contact or ingestion, **OR** one moderate or one severe symptom or sign but lacking information on time or mode of peanut contact [23].
[g]No history of a reaction; individuals were advised to avoid peanut due to testing **AND/OR** affected sibling, **OR** have no history of peanut exposure. A mild reaction was defined by pruritus, itchy throat, urticaria, flushing, or rhinoconjunctivitis. A moderate reaction was defined by angioedema, coughing, stridor, tight throat, voice change, nausea, abdominal pain, vomiting, or difficulty breathing. A severe reaction was defined by wheezing, cyanosis, or circulatory collapse [23].

associated with FA in two separate GWAS [22, 23]. LRRC32 is discussed further below [65]. Knockdown of *EMSY* expression is correlated with increased expression of skin barrier proteins in cell culture [66]. Additional loci for epithelial barrier genes have been identified in candidate gene studies and primary immunodeficiency disorders (Tables S1, S2).

3 | Genetic Loci Related to Immunity in Food Allergy

The most consistent genetic evidence for FA has been observed in the human leukocyte antigen (*HLA*) region on Chr6, which encodes the major histocompatibility complex responsible for presentation of antigenic peptides. *HLA* genes are implicated in many immunologically-mediated conditions and are imperative for antibody generation and IgE production [67]. Evidence for the involvement of *HLA* genes in FA is longstanding and includes both genome-wide and candidate gene studies [68]. *HLA* loci for FA that have been identified include *HLA-DPB1*, *HLA-DQA1, HLA-DQA2, HLA-DQB1, HLA-DRA*, and *HLA-DRB1* [69]. Although the mechanism through which *HLA* influences FA is unknown, *HLA* variants affect the presentation of non-self antigens or influence thymic selection for class II restricted T cell receptors [70, 71]. Interestingly, different association signals in the HLA class II gene cluster were found for two distinct wheat allergy phenotypes in the same population: iterative conditional analysis in the HLA region revealed three independent association signals for allergy to hydrolyzed wheat proteins with a coding variant in *HLA-DQA1* (rs9271588), the *HLA-DQA1*03:03* allele, and rs9263827 near *HLA-C* [27]. Conversely, wheat-dependent exercise-induced anaphylaxis was most strongly associated with the *HLA-DPB1*02:01:02* allele in the Japanese population [26]. *HLA-DPA1* is associated with wheat-dependent exercise-induced anaphylaxis [27]. *HLA-DPA1* has been also associated with AD [72]. Genome-wide significant association for self-reported shrimp and peach allergy was found upstream of *HLA-DQA1* in a large GWAS in 11,000 Japanese women [73]. Furthermore, the *HLA-DQB1* locus was linked to PA in four GWAS [22, 25, 50, 74]. However, the association in one of these studies did not meet the threshold of genome-wide significance, likely attributable to small sample size [50]. Due to the strong linkage disequilibrium at this locus, fine-mapping to pinpoint causal variants remains a challenge. Specific HLA haplotypes—a set of DNA variants that tend to be inherited together—may confer increased risk and are discussed elsewhere [75]. Hong et al. performed a detailed analysis of the region for PA and identified two functional variants that were associated with differential DNA methylation levels at multiple cytosine-phosphate-guanine (CpG) sites ($p < 5 \times 10^{-8}$), and differential DNA methylation of the *HLA-DQB1* and *HLA-DRB1* genes [25]. These results await replication, but provide a potential epigenetic mechanism through which genetic variants in the HLA region affect FA risk.

The same risk alleles at the *LRRC32* locus were associated with FA at genome-wide significance in two studies [22, 23] and were also associated with multiple atopic diseases, blood eosinophil counts, and other inflammatory disorders including ulcerative colitis (Table 3). The associated variant is located in an enhancer element that upon deletion in the syntenic chromosomal region in a mouse model abolished the expression of *LRRC32* in Tregs, rendering them incapable of suppressing colitis in the mouse [65]. Impaired Treg function is found in some Mendelian disorders with FA as a symptom (Table S1) [76].

Loci in the cytokine gene cluster at Chr5q31.1 are significantly associated with FA [22]. This region is also associated with AD, asthma, and the atopic march [77, 78]. The SNP rs11949166 is an intergenic variant flanked by *IL4* and kinesin family member 3A (*KIF3A*). IL-4 is a key cytokine in allergic diseases and upregulates IgE [79]; IL-4 is secreted by T-helper and type-2 innate lymphoid cells (ILC2), which leads to reduced allergen-specific Tregs [80, 81]. IL-4 production by ILC2s and splenocytes is enhanced by allergen sensitization through skin [82, 83]. ILC2s provide a link between innate and adaptive immunity, and are found in epidermal, gastrointestinal, and respiratory epithelial barriers [84]. *KIF3A* encodes a subunit of kinesin 2, a transporter protein [85]. *KIF3A* variants have been previously associated with both AD [86] and EoE [87].

Additional significant GWAS findings in novel genetic regions include an intronic variant found in angiopoietin 4 (*ANGPT4*), a pro-angiogenic factor [23] that stimulates eosinophil migration [88]. An intronic variant in the RNA binding fox-1 homolog 1 (*RBFOX1*) gene is a susceptibility locus in hydrolyzed wheat protein allergy [26] and CNVs in *RBFOX1* as well as catenin alpha 3 (*CTNNA3*) have been associated with FA in children [89].

Many additional candidate genes for FA exist based on diagnostic criteria that are difficult to differentiate from sensitization to food allergens, or have reached levels suggestive of significance ($p < 1 \times 10^{-5}$) but may have been impacted by sample size or other methodological limitations. These additional candidates have been covered in a previous systematic review of genetic determinants of FA and are shown in Table S2 [69, 90].

4 | Epigenetic Modifications Associated With Food Allergy

Epigenetic mechanisms affect gene expression without a change in the DNA sequence and can be inherited or acquired. Inherited epigenetic changes can be intergenerational (parent's germline is exposed to an environmental cue leading to offspring with same change), or transgenerational (change is inherited in further generations without direct contact with the environmental cue) [91]. Currently known epigenetic mechanisms include (Figure 1): (1) DNA methylation—addition of methyl groups to CpG sites (a cytosine nucleotide is followed by a guanine separated by a phosphate), (2) histone modification—modification of histones, often on the tail or the globular portion, changes the configuration of the histones to allow or deny access to DNA; (3) non-coding RNA (ncRNA)—RNA which does not make protein, but activates or represses genes, regulates post-translational processes, or acts on chromatin or methylation. Epigenetic changes can be regulated by DNA variants but also can be shaped by external factors, which may provide a mechanism through which FA is influenced by the environment [92–94].

Epigenetic research is affected by phenotyping issues as in all studies of FA [19], with some studies focusing on self-reported

FA [95], and others concentrating on general atopy [96]. Epigenetic studies have additional complexity as epigenetic signatures are dynamic and can be influenced by cell types, cell activation, sex, age [97], and exposures such as diet [98], and may represent causes but also consequences of FA [99]. Epigenetic marks are also contextual; their influence on gene expression depends on localization to promoters, gene bodies, CpG islands, or non-coding regions; this is particularly true for DNA methylation. These factors complicate interpretation of cross-sectional studies as well as comparisons across studies.

An increasing body of evidence highlights the association of epigenetic markers with disease risk, including candidate gene and epigenome-wide studies [100]. Most studies have focused on DNA methylation in easily accessible tissues (blood or blood-derived cells). Similar to genetic studies of FA, some have examined specific candidate genes for differential methylation (Table S3); few have taken an epigenome-wide approach. Two previous reviews identified candidate genes and epigenome-wide association studies (EWAS) of FA phenotype, without specific cut-offs for significance [100, 101]. Table 4 indicates the methylation sites that showed epigenome-wide significant association with FA according to the analysis method used ($p < 2.4 \times 10^{-7}$ for analyses with 450 k arrays and $p < 9 \times 10^{-8}$ for analyses with EPIC arrays) [102, 103]; only four studies showed CpGs associated with *p*-values under this threshold and also fulfilled phenotype criteria for this review (clinically diagnosed FA; sensitization-only phenotype excluded). Twenty CpG sites in CD4+ T-cells were associated with FA for pediatric hen's egg, cow's milk, or PA in one study that showed stability in methylation levels in the first 12 months of life [104]. Two of the other studies utilized peripheral blood DNA samples and examined pediatric cow's milk allergy. Of these, one study of cow's milk allergy defined by clinical history and laboratory testing identified 10 associated CpG sites [105], while the other with OFC criteria for FA identified a single CpG site that met the criteria outlined in this review, but this association was observed exclusively in females [106]. The fourth study analyzed methylation sites from peripheral blood mononuclear cells (PBMCs) and identified one CpG site associated with PA. The concern that employment of strict *p*-value thresholds in EWAS is overly conservative, combined with the small number of studies and the use of false discovery rate for correction of multiple testing [107, 108], has led us to include results that did not reach epigenome-wide significant associations, but used FA phenotypes with a false discovery rate (FDR) $< 1 \times 10^{-4}$. These have been included in Table 4. The functions of genes associated with the closest transcription start sites to these CpG sites are discussed below.

5 | Epigenetic Loci Related to Epithelial Barrier Function in Food Allergy

Several CpG sites identified in EWAS studies of FA are linked to epithelial barrier or skin integrity, including a CpG in the promoter region of late cornified envelope 3A (*LCE3A*) and two in the 3′UTR region of delta 4-desaturase, sphingolipid 2 (*DEGS2*) [104, 105]. Part of the antimicrobial barrier [112], *LCE3A* expression is induced by skin injury or inflammation [113, 114]. *DEGS2* is involved in the sphingolipid synthesis in skin and other sphingolipid-containing tissues [115]. Disruption of metabolism [116, 117] or altered response to sphingolipid metabolites has been noted in FA [118], EoE [119], and asthma-risk genotypes [120].

Some FA-associated CpG sites appear related to cell migration, including those in the genes of Enah/Vasp-like (*EVL*), cell division cycle associated 7 (*CDCA7*), and prostaglandin F2 receptor inhibitor (*PTGFRN*), and one upstream from the transcription site of pleckstrin homology and RhoGEF domain containing G4B (*PLEKHG4B*) [104, 105]. *EVL* is involved in epithelial and immune cell migration [121] and along with *PLEKHG4B* [122] has a role in actin assembly [123] *CDCA7* inhibits epithelial-mesenchymal transition [124]; it also has a CNV [125]. Contactin 6 (*CNTN6*) [126], cell adhesion molecule L1 like (*CHL1*) [127], and *PTGFRN* encode cell adhesion molecules [128]. *EDARADD* defects cause ectodermal dysplasia, with abnormal development of hair, teeth, and nails, and may be accompanied by dry skin and eczema [129]. Another locus with FDR $< 1 \times 10^{-4}$, FERM domain containing kindlin 3 (*FERMT3*), has been identified as a cause of leukocyte adhesion deficiency III [130].

Other significant CpGs linked to genes involving skin or epithelial function include those in the promoter region of *keratin associated protein 5–7* (*KRTAP5-7*) and the gene body of zinc finger FYVE-type containing 28 (*ZFYVE28*) [104], which encodes a protein that modulates epidermal growth factor signaling [131]. Genes in the *KRTAP* family are involved in hair formation; however, *KRTAP* homologs are present in hairless organisms, suggesting *KRTAP5-7* could have a more complex role [132].

6 | Epigenetic Loci Related to Immunity in Food Allergy

Several CpGs identified with genome-wide significance for FA occur in or near important cytokines, including CpG sites upstream of the transcription start sites of *IL4* and IL1 receptor like 1 (*IL1RL1*), in the 5′UTR of IL-5 receptor alpha subunit (*IL5RA*), and in the gene body of C-C motif chemokine ligand 18 (*CCL18*) [105]. *IL4* is of particular interest as this gene also achieved genome-wide significance in GWAS of FA [22]. *IL4*, and its flanking gene *IL13*, are key cytokines in AD [133], asthma [134], EoE [135], and AR [136]. A CpG site significant for FA was also identified in the nedd4 family interacting protein 2 (*NDFIP2*) gene [105], the expression of which is regulated by IL-4 during Th2 cell differentiation [137]. *NDFIP2* promotes interferon gamma (IFNγ; *IFNG*) production by Th1 cells [137].

Support for the *IL5RA* locus in FA primarily exists through studies of its ligand, IL-5, which is important in eosinophil function [138]. Methylation of *IL5RA* in blood of asthmatic children was correlated with eosinophilia [139]. Differential expression of *IL5* was found in PBMCs of children with egg allergy [140]. *IL5* was consistently overexpressed in children and adolescents who have concomitant comorbidities of asthma, AD, and AR [141] and was differentially methylated in a study of allergic diseases [142]. Elevated childhood plasma levels of CCL18 precede the development of allergy and asthma [143] and CCL18, along with many other Th2-related cytokines, was upregulated in skin biopsies of AD patients [144].

TABLE 4 | Significant epigenetic variants associated with clinically diagnosed food allergy at epigenome-wide level or at false discovery rate value $<1\times10^{-4}$.

CpG ID[a]	Chr	Position[b]	Flanking coding genes Nearest gene transcription start site in bold	Location	Closest coding gene	Cell type/technolog	*p* or FDR value[c]	Study population	Diagnostic criteria	Reference
Epigenome-wide significant epigenetic variants										
cg16060930	1	117487269	***PTGFRN***-*CD101*	Gene body	*PTGFRN*	CD4+ T-cells/450k array	1.9×10^{-8}	**(I)** Australia/no mention of ethnicity 12 children that developed IgE food allergy at 12 months Longitudinally collected DNA samples at birth and 12 months Boys, n (%): 9 (75.0)	**(I)** **Food allergy** SPT (size n/r) and allergic symptoms (respiratory involvement, angiodema, urticaria) on exposure determined by questionnaire data	Martino[d] [104]
cg22505202	1	95088560	***F3***-*SLC44A3*	Intergenic	*F3*	CD4+ T-cells/450k array	6.2×10^{-8}			Martino[d] [104]
cg20960322	1	182002021	*CACNA1E*-***ZNF648***	Intergenic	*ZNF648*	CD4+ T-cells/450k array	7.0×10^{-8}			Martino[d] [104]
cg16046605	1	152596413	***LCE3A***-*LCE2D*	TSS1500	*LCE3A*	CD4+ T-cells/450k array	6.2×10^{-8}			Martino[d] [104]
cg06221963	1	154839813	***KCNN3***-*PMVK*	Gene body	*KCNN3*	CD4+ T-cells/450k array	9.4×10^{-8}			Martino[d] [104]
cg01802772	1	55014160	***ACOT11***-*FAM151A*	Gene body	*ACOT11*	CD4+ T-cells/450k array	1.0×10^{-7}			Martino[d] [104]
cg16386158	2	102927398	*IL1RL2*-***IL1RL1***	TSS1500	*IL1RL1*	Whole peripheral blood/450k array	1.7×10^{-13}	**(II)** *Discovery stage*: USA/Caucasian 106 children Age (years) (mean ± SD): 4.2 ± 2.7; Boys, *n* (%): 67 (63.2) *Replication stage*: USA/Caucasian five children; Age (years) (mean ± SD): 7.2 ± 4.1; Boys, *n* (%): 4 (80.0) USA/African-American eight cord blood samples; Age (years) (mean ± SD): 3.8 ± 2.1; Boys, *n* (%): 5 (62.5)	**(II)** **Cow's milk allergy** (1) a convincing history of symptoms indicative of an allergic reaction within 2 h of ingestion and (2) clear evidence of *sensitization* defined as having a specific IgE level of > 0.35 kU/L and/or (3) positive SPT (wheal diameter > 3 mm)	Hong [105]
cg13316148	2	191916269	***STAT1***-*STAT4*	Gene body	*STAT4*	Whole peripheral blood/450k array	6.3×10^{-9}			Hong [105]
cg08995061	2	174129462	*MAP3K20*-***CDCA7***	Gene body	*MAP3K20*	CD4+ T-cells/450k array	6.2×10^{-8}	See entry **(I)**	See entry **(I)**	Martino[d] [104]
cg02887598	2	127841945	***BIN1***-*CYP27C1*	Gene body	*BIN1*	CD4+ T-cells/450k array	4.5×10^{-8}			Martino[d] [104]
cg08404225	3	3151900	***IL5RA***-*TRNT1*	5′UTR	*IL5RA*	Whole peripheral blood/450k array	9.3×10^{-10}	See entry **(II)**	See entry **(II)**	Hong [105]

(Continues)

TABLE 4 | (Continued)

CpG ID[a]	Chr	Position[b]	Flanking coding genes Nearest gene transcription start site in bold	Location	Closest coding gene	Cell type/technolog	*p* or FDR value[c]	Study population	Diagnostic criteria	Reference
cg01601518	4	2404284	***ZFYVE28***-*CFAP99*	Gene body	*ZFYVE28*	CD4+ T-cells/450 k array	1.2×10^{-9}	See entry **(I)**	See entry **(I)**	Martino[d] [104]
cg19311470	4	39460490	***RPL9***-*LIAS*	5′UTR-TSS1500	*RPL9*	CD4+ T-cells/450 k array	1.5×10^{-7}			Martino[d] [104]
cg21874902	5	33727007	***ADAMTS12***-*RXFP3*	Gene body	*ADAMTS12*	CD4+ T-cells/450 k array	4.6×10^{-9}			Martino[d] [104]
cg26787239	5	132008525	*IL13*-***IL4***	TSS1500	*IL4*	Whole peripheral blood/450 k array	6.7×10^{-9}	See entry **(II)**	See entry **(II)**	Hong [105]
cg12869097	5	80493	Chromosome start-***PLEKHG4B***	Intergenic	*PLEKHG4B*	CD4+ T-cells/450 k array	1.6×10^{-8}	See entry **(I)**	See entry **(I)**	Martino[d] [104]
cg15090899	6	167178260	*MPC1*-***RPS6KA2***	Gene body	*RPS6KA2*	Whole peripheral blood/450 k array	3.6×10^{-8}	See entry **(II)**	See entry **(II)**	Hong [105]
cg06330797	6	167195910	***RPS6KA2***-*RNASET2*	Gene body	*RPS6KA2*	CD4+ T-cells/450 k array	5.1×10^{-8}	See entry **(I)**	See entry **(I)**	Martino[d] [104]
cg23586565	7	135457413	***FAM180A***-*MTPN*	Intergenic	*FAM180A*	PBMCs/EPIC array	$<9\times10^{-8}$	**(III)** Germany/no mention of ethnicity six adult cases seven adult controls without atopy or PA age at sampling (years, mean ± SD): cases: 29.2 ± 2.9; controls: 32.4 ± 2.1 Males: *n* (%): cases: 3 (50); controls: 1, (14)	**(III)** **Peanut allergy** History of systemic allergic reactions after peanut consumption through double-blind placebo-controlled food challenges	Worm [109]
cg09377531	8	141046469	***KCNK9***-*TRAPPC9*	Gene body	*TRAPPC9*	Whole peripheral blood/450 k array	7.0×10^{-14}	See entry **(II)**	See entry **(II)**	Hong [105]
cg06894070	11	71238205	*NADSYN1*-***KRTAP5-7***	TSS1500	*KRTAP5-7*	CD4+ T-cells/450 k array	5.9×10^{-14}	See entry **(I)**	See entry **(I)**	Martino[d] [104]
cg23876832	11	62092739	*SCGB1D4*-***ASRGL1***	Intergenic	*ASRGL1*	Whole peripheral blood/450 k array	1.7×10^{-7}	**(IV)** Netherlands/no mention of ethnicity 20 children Age (years) (mean ± SD) at diagnosis: 6.5 ± 2.5, at sampling: 11.8 ± 4.8; Boys, *n* (%): 8 (40.0)	**(IV)** **Cow's milk allergy** Serum specific IgE > 0.35 kU/L and a double-blind placebo-controlled food challenge	Petrus [106]

(Continues)

TABLE 4 | (Continued)

CpG ID[a]	Chr	Position[b]	Flanking coding genes Nearest gene transcription start site in bold	Location	Closest coding gene	Cell type/technolog	*p* or FDR value[c]	Study population	Diagnostic criteria	Reference
cg25824218	12	25104798	***BCAT1***-*IRAG2*	Intergenic	*BCAT1*	CD4+ T-cells/450k array	7.1×10^{-8}	See entry **(I)**	See entry **(I)**	Martino[d] [104]
cg11770323	13	80066032	*RBM26*-***NDFIP2***	Gene body	*NDFIP2*	Whole peripheral blood/450k array	2.0×10^{-15}	See entry **(II)**	See entry **(II)**	Hong [105]
cg16409452	14	100610186	*EVL*-***DEGS2***	3′UTR	*EVL*	Whole peripheral blood/450k array	5.6×10^{-14}			Hong [105]
cg18550847	14	100610571	*EVL*-***DEGS2***	3′UTR	*EVL*	Whole peripheral blood/450k array	9.6×10^{-14}			Hong [105]
cg11857805	14	100441223	*EML1*-***EVL***	Gene body	*EVL*	CD4+ T-cells/450k array	1.2×10^{-8}	See entry **(I)**	See entry **(I)**	Martino[d] [104]
cg08923669	16	420230	***MRPL28***-*PGAP6*	5′UTR	*MRPL28*	CD4+ T-cells/450k array	3.6×10^{-8}			Martino[d] [104]
cg02978201	16	11374865	*PRM2*-***PRM1***	Gene body	*PRM1*	CD4+ T-cells/450k array	2.2×10^{-7}			Martino[d] [104]
cg06040872	17	34394215	***CCL18***-*CCL3*	Gene body	*CCL18*	Whole peripheral blood/450k array	4.0×10^{-9}	See entry **(II)**	See entry **(II)**	Hong [105]
cg17662493	22	45806309	***SMC1B***-*RIBC2*	Gene body	*SMC1B*	CD4+ T-cells/450k array	8.9×10^{-8}	See entry **(I)**	See entry **(I)**	Martino[d] [104]
cg07972762	22	33196384	*SYN3*-***TIMP3***	Gene body-TSS1500	*SYN3*	CD4+ T-cells/450k array	7.2×10^{-11}			Martino[d] [104]
Significant epigenetic variants at false discovery rate value $<1\times10^{-4}$										
cg16240480	1	236557473	*ERO1B* -***EDARADD***	Intergenic	*EDARADD*	CD4+ T-cells/450k array	2.1×10^{-5}	**(V)** *Discovery stage:* USA/no mention of ethnicity 21 children Age (years) (mean ± SD): 11.0 ± 5.0 Boys, *n* (%): 14 (66.7) *Replication stage:* USA/no mention of ethnicity 19 children Age (years) (mean ± SD): 12.0 ± 4.0 Boys, *n* (%): 12 (63.2)	**(V)** **Peanut allergy** (1) reaction to peanut challenge during randomized, double-blind, placebo-controlled food challenges (2) a threshold-weighted reaction severity score calculated as the product of symptom grade and dose factor	Do[e] [110]
cg13500877	2	157,183,755	***NR4A2***-*GPD2*	Gene body	*NR4A2*	CD4+ T-cells/450k array	1.2×10^{-5}			Do[e] [110]
cg14771077	4	1166824	***SPON2***-*CTBP1*	Gene body	*SPON2*	CD4+ T-cells/450k array	9.0×10^{-5}			Do[e] [110]
cg05643286	4	4,173,660	*FAM86EP* -***OTOP1***	Intergenic	*OTOP1*	CD4+ T-cells/450k array	7.0×10^{-5}			Do[e] [110]
cg14738290	6	29,690,998	*ZFP57*-***HLA-F***	Intergenic	*HLA-F*	CD4+ T-cells/450k array	2.4×10^{-5}			Do[e] [110]
cg00225196	8	37,556,863	***ZNF703***-*ERLIN2*	3′UTR	*ZNF703*	CD4+ T-cells/450k array	3.9×10^{-6}			Do[e] [110]
cg24337701	8	141,275,191	***TRAPPC9***-*CHRAC1*	Gene body	*TRAPPC9*	CD4+ T-cells/450k array	6.1×10^{-5}			Do[e] [110]
cg09328083	11	44,286,477	*EXT2*-***ALX4***	Gene body	*ALX4*	CD4+ T-cells/450k array	4.1×10^{-5}			Do[e] [110]

(Continues)

TABLE 4 | (Continued)

CpG ID[a]	Chr	Position[b]	Flanking coding genes Nearest gene transcription start site in bold	Location	Closest coding gene	Cell type/technolog	*p* or FDR value[c]	Study population	Diagnostic criteria	Reference
cg18566095	11	63,982,675	***FERMT3***-*TRPT1*	Gene body	*FERMT3*	CD4+ T-cells/EPIC array	1.3×10^{-5}	**(VI)** Australia/Mixed ethnicity 44 mono-sensitized children Age at diagnosis: 11–15 months Boys, *n* (%): 21 (47.7)	**(VI)** **Egg allergy** (1) oral food challenge and skin prick testing for egg white, peanut, sesame and (cow's milk or shrimp) (2) follow-up at 2 or 4 years old to determine if children have transient or persistent egg allergy	Martino [111]
cg02251771	11	93,913,200	***PANX1***-*IZUMO1R*	Gene body	*PANX1*	CD4+ T-cells/450k array	1.3×10^{-5}	See entry **(V)**	See entry **(V)**	Do[e] [110]
cg14502395	11	128,318,562	*KIRREL3*-***ETS1***	Intergenic	*ETS1*	CD4+ T-cells/EPIC array	9.5×10^{-5}	See entry **(VI)**	See entry **(VI)**	Martino [111]
cg04361926	16	89,070,185	***CBFA2T3***-*ACSF3*	Intergenic	*CBFA2T3*	CD4+ T-cells / 450k array	9.0×10^{-6}	See entry **(V)**	See entry **(V)**	Do[e] [110]
cg13198297	17	18,046,564	***MYO15A***-*ALKBH5*	Gene body	*MYO15A*	CD4+ T-cells/450k array	2.5×10^{-6}			Do[e] [110]
cg12592365	17	78,765,948	***RPTOR***-*CHMP6*	Gene body	*RPTOR*	CD4+ T-cells/EPIC array	2.9×10^{-5}	See entry **(VI)**	See entry **(VI)**	Martino [111]

Abbreviations: 3′UTR, three prime untranslated region, section of messenger RNA (mRNA) that immediately follows the translation termination codon; 5′UTR, five prime untranslated region, section of mRNA that is upstream from an initiation codon; PA, peanut allergy; PBMC, peripheral blood mononuclear cells; PMID, PubMed publication identification number; TSS1500, the region 1500 base pairs upstream of the transcription start site.

[a]CpG ID according to Illumina's annotation.

[b]CpG position from the *Homo sapiens* Genome Reference Consortium Human Build 37 (hg19).

[c]Epigenome-wide threshold of $p<2.4\times10^{-7}$ calculated for 450k array according to Saffari et al. 201,872 and of $p<9\times10^{-8}$ calculated for Epic array according to Mansell et al. [103].

[d]Unadjusted *p* values were not available so adjusted *p* values below significance threshold were considered.

[e]False discovery rate (FDR) values for each CpG were not available (only FDR cutoff used) so unadjusted *p* values among CpGs with FDR < 0.05 and below significance threshold were considered.

The toll-like receptor IL1RL1 and its ligand IL-33 are associated with FA [145]. These play a role in airway exposure-induced PA in mouse models [146] and anaphylaxis to food in epicutaneously sensitized mice [147]. However, the functional role of this ligand and receptor in FA is unclear. *IL1RL1* SNPs were associated with peanut and hen's egg sensitization but not FA, and disease-associated SNPs in *IL1RL1* correlate with *IL1RL1* messenger RNA (mRNA) and serum protein levels of IL-1RL1a in asthma [148] but not in FA [149]. In a novel hyper-IgE syndrome characterized by FA, EoE, and asthma, duplication of the *IL33* region was not associated with any changes in circulating peripheral IL-33 or soluble IL1RL1 levels, despite increased *IL33* gene expression [150].

Other loci reaching epigenome-wide significance for FA include a CpG site located in the gene body of the signal transducer and activator of transcription 4 (*STAT4*) gene, near the transcription site for *STAT1*. *STAT4* skews toward Th1 expression, and binds multiple target sites on the genome [151]. *STAT1* is overexpressed in ileal mucosa of patients with asthma [152] and has been implicated in steroid resistance in murine models of airway inflammation [153] and AR [154]. *STAT1* gain of function can cause chronic mucocutaneous candidiasis [155].

Ribosomal protein S6 kinase A2 (*RPS6KA2*) encodes a serine–threonine kinase, and a methylation site in this gene (cg15090899) reached epigenome-wide significance for cow's milk allergy [105]. The same locus, but a different CpG site (cg05068730), was also observed in an EWAS of food sensitization in mid-childhood [95], but this locus had increased methylation compared to controls whereas less methylation was significant at cg15090899 in FA. Other CpG sites at this locus (cg06330797, cg03120116) have been identified in relation to food sensitization [104] and FA at 12 months of age [110]. Another significant locus, trafficking protein particle complex subunit 9 (*TRAPPC9*), was associated with FA in two EWAS [105, 110], highlighting its possible role in FA, although its function is unknown [105].

Significant CpGs for FA have been identified near genes for a metalloproteinase (ADAM metallopeptidase with thrombospondin type 1 motif 12; *ADAMTS12*) and an inhibitor of matrix metalloproteinase (TIMP metallopeptidase inhibitor 3; *TIMP3*) [104]. *ADAMTS12* is a disintegrin with a role in asthma and allergic inflammation [156, 157] *TIMP3* encodes a protease that targets extracellular matrix [158], a process important to airway remodeling in asthma [159, 160]. *TIMP3* gene expression was increased in sputum samples of patients with mild to moderate asthma compared to controls [161]. Two EWAS identified 11 PA-associated CpG sites [110] and 4 egg allergy-associated CpG sites with FDR $< 1 \times 10^{-4}$ [111]. Six of the 15 genes with the nearest transcription site are linked to atopic diseases, likely through immune response mechanisms or regulation of lymphocyte function. These conditions include (1) asthma: ETS proto-oncogene 1, transcription factor (*ETS1*) [162], major histocompatibility complex, class I, F (*HLA-F*) [163], pannexin 1 (*PANX1*) [164], regulatory associated protein of MTOR complex 1 (*RPTOR*) [165], and spondin 2 (*SPON2*) [166]; (2) AR: *ETS1* [167], nuclear receptor subfamily 4 member a2 (*NR4A2*) [168], and (3) AD: *ETS1*, *NR4A2* [169, 170].

Several genes linked to methylation sites are relatively unknown in the FA literature but are related to other allergic diseases or immune function, such as response to bacteria [171, 172]; these include CpGs in the 5′UTR of ribosomal protein L9 (*RPL9*), and near coagulation factor III, tissue factor (*F3*) [104]. Expression of family with sequence similarity 180 member A (*FAM180A*) is regulated by TGFB [173]; an intergenic CpG near *FAM180A* was significantly associated with PA [109]. The mitochondrial ribosomal protein L28 (*MRPL28*) [174] has a FA-associated CpG located in its 5′UTR [104]; a different CpG in the first exon had increased methylation in infants exposed to maternal asthma during pregnancy [175]. A CpG located near the transcription start site of branched chain amino acid transaminase 1 (*BCAT1*) is significant for FA [104]. Its gene expression and protein levels were increased in OVA-challenged mice, and inhibition of *BCAT1* decreased airway remodeling and levels of autophagy markers [176, 177]. *RPTOR* and *NR4A2* may be involved in autophagy [178, 179], Autophagy genes are associated with asthma prognosis, progression, and remodeling [180, 181], and intertwined with apoptosis [182, 183]. CpG sites in genes associated with apoptosis are also significant in FA, including a CpG in the promoter region of lipoic acid synthetase (*LIAS*) [184], and the gene body of bridging integrator 1 (*BIN1*) [104, 185], as well as *RPS6KA2* [105, 186].

7 | Epigenetic Loci Currently Unrelated to Immunity and Barrier Function

The remaining CpGs associated with FA correspond with genes that have no known relationship to barrier, immunity or atopy. Many of these loci are involved in growth, development, and cell division or proliferation, or have roles in metabolism or signaling [187–200].

8 | Integration of Genetic and Epigenetic Findings in Food Allergy and Knowledge Gaps

Some identified risk loci have both genetic and epigenetic associations with FA (Tables 3, 4), including *IL4* which was a significant locus both in EWAS and GWAS of FA [22, 105]. Other loci, including *HLA* and *FLG* have genome-wide or epigenome-wide significance with candidate gene or longitudinal studies supporting their role in FA (Tables S2, S3). *HLA* has multiple significant risk loci from GWAS and candidate gene studies, with smaller studies showing DNA methylation at *HLA-DQB1* and *HLA-DRB* [104, 105]. DNA methylation may regulate *FLG* transcription [201], although this has not yet been shown in FA [202]. DNA methylation has been the main focus of epigenetic studies of FA, but other mechanisms may play a role, including histone modification [196], and ncRNA [203–206], which have links to loci identified through GWAS [22–24]. Alternative splicing can be influenced by epigenetic marks [207, 208]; and *RBFOX1*, a GWAS locus [26], belongs to a family of proteins that regulates tissue-specific alternative splicing [209]. Work on desensitization and development of natural tolerance may also provide insight into epigenetic mechanisms in the pathogenesis of FA [104, 111, 210–212]. However, it may be unclear whether observed changes are cause or effect.

9 | Gene–Environment Interactions in Food Allergy

Gene–environment interactions are key to development of FA, sensitization to food, or tolerance. This has primarily been investigated with regards to diet, peanut allergen exposure, and vitamin D. Children with high levels of environmental cutaneous exposure to peanut allergen, as measured by peanut dust, had an incremental increased risk of sensitization to peanut in individuals with known *FLG* LoF mutations [53, 54]; this dose–response relationship was not seen in individuals with wildtype *FLG*. *MALT1* risk allele carriers who avoided oral peanut exposure were more likely to develop PA, indicating it may be an independent risk factor for PA in individuals who avoid peanut. This carrier effect was abrogated by the intervention of early oral peanut exposure [213]. Polymorphisms that lower vitamin D binding protein (and thus increase vitamin D serum levels) have also been studied in infants, with maternal antenatal vitamin D supplementation associated with less FA, particularly with the GT/TT genotype, which lowers vitamin D binding protein [214]. Further work is needed regarding gene–environment interactions in FA.

10 | Population Differences and Diagnostic Criteria: Implications for Future Research

Ethnicity and socioeconomic status are correlated with FA [215]. Most genetic studies of FA were completed on individuals of self-identified Caucasian or Western European ancestry. *HLA* SNPs rs7192 and rs9275596 were significantly associated with PA in Caucasians, but not in individuals of non-European ancestry [25]. While the sample size was small, the direction of the effect of the OR of rs9274496 was actually opposite, with an OR of 0.6 in non-European compared to 1.7 in European ancestry [25]. This suggests that distinctions exist in genetic risk loci for FA in populations from different genetic ancestry, which may be due to difference in LD structure of these populations, a phenomenon that has also been described in other atopic diseases [216–220]. Epigenetic differences between populations can be caused by genetic factors or environmental exposures, or a combination of both [221], but the majority of ancestry-related DNA methylation variation is driven by genetic factors [222]. Seafood allergy is more common in Asian and Hispanic than in White populations [223]. This may be due to genetic variation, or could point to the role of different diets or other allergen exposures [224, 225], providing distinct gene by environment interactions across different populations. Approximately 25% of the variation in gene expression in a study of individuals sampled for human genome diversity panel could be attributed to population differences [226]. Differences in DNA methylation of populations of diverse ethnicity have been identified in several studies [227–229]; this may be attributed to both genetic and environmental influences [227]. A strong evidence base for FA genetics and epigenetics in diverse and admixed populations is lacking, which supports the call for more diversity in FA genetic research and should be reflected in GWAS and EWAS chip design [217, 230]. Increasing diversity in chip design is especially important given the rise of FA in developing nations [231] and the complexity of diagnosis and management of FA in regions subject to food insecurity and limited health care infrastructure [232].

Research has been complicated by difficulties in defining FA based on clinical history and laboratory cut-offs, including skin prick test (SPT) and specific immunoglobulin E (sIgE), in the absence of an oral food challenge, prompting us to create proposed groups of FA phenotypes for future large-scale genetic studies [19]. The interwoven nature of allergic diseases adds complexity that can limit the ability to detect specific genetic variants for FA versus general allergic disease risk. Researchers must also decide on whether to combine all types of FA together or focus on allergies to a specific type of food. It is yet unknown if an allergy to a specific food is driven by an environmental exposure interacting with a general susceptibility to FA, or if genetic and epigenetic risk factors for specific FA exist. Studies can be designed with the assumption that the underlying genetic model involves specific risk loci for specific foods, or that all FA are influenced by the same specific risk loci. Grouping all FA together, which is often done to maximize sample size and increase power, may favor identification of general susceptibility loci but obscure loci for specific food allergens.

11 | Prevention and Treatment of Food Allergy and Role of (Epi)-genetics: Future Directions

Primary prevention of FA centers around timing of introduction to foods and regular ingestion during infancy [233–235], and has been shown to significantly reduce development of PA in children both with and without AD [236, 237], with data supporting this premise for cow's milk [238–240], cashew [241] and egg [242]. Development of tolerance to one allergen does not prevent the development of FA to another food [243]. Current guidelines suggesting early oral introduction are suitable for the general population [244]. However, up to 12% of infants at higher risk may already be allergic at time of food introduction [245–247].

The mainstay of secondary prevention and treatment of FA is immunotherapy. Previously management relied on allergen avoidance and treatment of exposure with epinephrine [248]; it is now estimated that 80% of children [245–247, 249] can be desensitized through gradual, medically supervised introduction of the allergen [247, 250]. Established protocols exist for oral immunotherapy (OIT) [247, 251] and further evidence for immunotherapy continues to accrue [252], including adjuvant therapy [253]. Immunotherapy is resource-intensive, requires access to allergists [254], and can have risks to patients [245, 255]. In addition to the influence *HLA* has on FA susceptibility, outlined above, specific *HLA* alleles have been investigated in PA desensitization and maintenance of tolerance. *HLA-DQA1*01:02* has a protective role against PA in the setting of peanut consumption, but is a risk allele if peanut is avoided [256]. A higher proportion of carriers of *HLA-DQA1*01:02* receiving OIT were desensitized compared to non-carriers (93% vs. 78%; OR 5.74, $p = 0.06$) in a study of 126 children aged 12–<48 months [257]. Other factors such as age and prior sensitization likely play a role in success of OIT; while not significant, *HLA-DQA1*01:02* carriers more frequently attained continued desensitization and sustained unresponsiveness than non-carriers in a cohort aged 7–55 years (80% vs. 61% for continued desensitization and 52% vs. 31% for sustained unresponsiveness) [257]. Genetic or epigenetic risk scores [258] could be a tool to guide decisions regarding optimal management, such as identifying those at highest risk in order

to intervene earlier, those most likely to have side effects from oral immunotherapy such as severe reactions or EoE, and those most likely to achieve sustained unresponsiveness.

12 | Conclusion

An improved ability to distinguish predict, diagnose, and characterize FA would benefit clinical management and research. Evaluation of shared and distinct pathways in atopic diseases is necessary to reveal potential targets for future treatments. The pathways currently identified through large-scale studies on FA include epithelial barrier and immune function. Genetic and epigenetic markers may ultimately offer ways to predict the presence or absence of clinical IgE-mediated FA among sensitized individuals [19, 259], or likelihood of development of natural tolerance and response to immunotherapy. Further research is required in specific populations and to elucidate the mechanisms through which these markers elicit their effects.

Author Contributions

All authors listed are members of the InFAC consortium and each author has met the criteria for authorship.

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Conflicts of Interest

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investigator initiated oral immunotherapy trials supported by the Food Allergy and Anaphylaxis Program Sickkids and serve as associate editor for Allergy. he recently was and is acting site PI of company sponsored trials by DBV, Novartis and Stallergen. LS, CL, MS, BLT, AMM, MBS, AEC, DV, CH, AJS, BFW, AB, AE, AAS, YS, ET, GK, DD, DM, SE, JG, VS, BDM, and YL report no conflicts of interest.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.