

Current insights into the genetics of food allergy



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Food allergy (FA), a growing public health burden in the United States, and familial aggregation studies support strong roles for both genes and environment in FA risk. Deepening our understanding of the molecular and cellular mechanisms driving FAs is paramount to improving its prevention, diagnosis, and clinical management. In this review, we document lessons learned from the genetics of FA that have aided our understanding of these mechanisms. Although current genetic association studies suffer from low power, heterogeneity in definition of FA, and difficulty in our ability to truly disentangle FA from food sensitization (FS) and general atopy genetics, they reveal a set of genetic loci, genes, and variants that continue to implicate the importance of barrier and immune function genes across the atopic march, and FA in particular. The largest reported effects on FA are from *MALT1* (odds ratio, 10.99), *FLG* (average odds ratio, ~2.9), and *HLA* (average odds ratio, ~2.03). The biggest challenge in the field of FA genetics is to elucidate the specific mechanism of action on FA risk and pathogenesis for these loci, and integrative approaches including genetics/genomics with transcriptomics, proteomics, and metabolomics will be critical next steps to translating these genetic insights into practice. (*J Allergy Clin Immunol* 2021;147:15-28.)

Key words: Food allergy, peanut allergy, genetics, genomics, barrier genes, immune genes, atopic march, Dual Allergen hypothesis, FLG, HLA

Abbreviations used

AD: Atopic dermatitis
AR: Allergic rhinitis
CGAS: Candidate gene association study
CMA: Cow's milk allergy
DZ: Dizyotic
EA: Egg allergy
EDC: Epidermal differentiation complex
EoE: Eosinophilic esophagitis
FA: Food allergy
FLG: Filaggrin
FS: Food sensitization
GOFA: Genetics of Food Allergy
GWAS: Genome-wide association study
G × E: Gene × Environment
LD: Linkage disequilibrium
LEAP: Learning Early About Peanut Allergy
LOF: Loss-of-function
MZ: Monozygotic
NR: Not reported
OFC: Oral food challenge
OR: Odds ratio
PA: Peanut allergy
ps: Peanut-specific
sIgE: Specific IgE
SNP: Single nucleotide polymorphism

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Terms in boldface and italics are detailed in the glossary on page 16.

Food allergy (FA) is a growing public health burden in the United States and globally.¹ Upon exposure to an allergenic food protein, the immune system mounts a response by producing antigen-specific IgE (sIgE), a state termed as food sensitization (FS). On reexposure, the allergenic food binds to specific antibodies and triggers the release of mediators, such as histamine, leading to symptomatic FA.² The **Dual Allergen Exposure hypothesis**, which states that low-dose cutaneous sensitization to food may lead to FS and early consumption of food may induce oral tolerance,³ is one proposed hypothesis for increases noted in FA prevalence.³ In addition, the mechanism of FA development as illustrated through the **atopic march** suggests a role for both barrier and immune-related genes given the hypothesis that children predisposed to atopic dermatitis (AD) or FA in early childhood have an increased risk of developing other allergic diseases such as asthma and allergic rhinitis (AR) later in life.^{4,5} The pathophysiology of FA development is therefore a complex interplay of environmental factors, including allergen exposure, within a strong interaction framework with genetic risk factors.^{3,6}

Although there have been a wide array of genetic studies on FA spanning different approaches (Box 1) as detailed in Table E1 in

Box 1. Key approaches used in genetic studies of complex diseases

- **Familial aggregation studies:** The often relied-on first line of evidence in documenting a genetic component to disease interrogating whether clustering within families is greater than the general population prevalence.
- **Heritability:** The quantification of the overall phenotypic variation/risk that is attributable to genetic factors.
- **Association testing:** Tests for the correlation between disease and genetic markers (most often single nucleotide polymorphisms [SNPs]) typically in a case-control design setting wherein allele frequencies at a measured SNP are compared between case and control samples from the population.
- **Candidate gene association studies (CGASs):** Targeted studies of association between selected genes of interest and a phenotype. The approach begins with selection of a putative candidate gene on the basis of its relevance in the mechanism of the disease or trait being investigated and are most often performed in the framework of a case-control study.
- **Genome-wide association study (GWAS):** Relies on the idea that common genetic variation across the genome is correlated in blocks because of linkage disequilibrium, and their measuring approximately 2.5 million genetics variants on a high throughput assay can capture most associations with common variants.
- **Gene $\times$ Environment ($G \times E$) interactions:** Interrogate how environmental exposures and genetic predisposition work together to modify disease risk and/or outcome. An interaction is indicated when the presence of one factor (eg, lifestyle and diet) affects the influence of the second factor (eg, genetic) on disease risk.
- **Whole-exome sequencing (WES) and whole-genome sequencing (WGS):** Two next-generation sequencing techniques to study the common and rare genetic variations in the genome. WES allows variations in the protein-coding region of any gene to be identified, whereas WGS offers the ability to interrogate the entire DNA sequence of the genome.
- **Meta-analysis:** A routine approach to combining smaller GWAs using summary statistics/results to overcome the smaller sample sizes of individual studies.
- **Fine-mapping:** A set of statistical and laboratory approaches to determine the causal genetic variant for associated genetic loci.

this article's Online Repository at www.jacionline.org, there are several challenges with these that need to be articulated before evaluating the evidence for FA loci for their robustness, and interpretation of their effects on FA risk. First, very few studies adequately measure environmental exposure either *in utero* or early life. Therefore, they are unable to capture **Gene $\times$ Environment ($G \times E$) interactions**. In a disease in which the interaction between genes and environment may be quite large, this could result in a major loss in power to fully identify FA genetic determinants. Studies to date are further limited in power with small sample sizes; the largest study is approximately 11,000 samples (Table E1). Where potential exists for **meta-analysis** approaches to overcome the weaknesses of smaller studies, the existing studies are highly variable in definition of outcome ranging from health questionnaires, skin prick testing, quantitative biomarkers (eg, sIgE) to double-blind placebo-controlled oral food challenges (OFCs). In addition to variability in the definition of FA cases, there is variability in the definition of controls (eg, atopic vs nonatopic controls vs unphenotyped population-based controls; Table E1). Overall, there is difficulty in teasing

apart FA from FS genetics across these studies, and the range of phenotype definition introduces heterogeneity in disease outcome for any combined meta-analysis approach across them. Despite these limitations, there have been numerous genetic loci, many with robust replication, suggested for FA (Table I),⁷⁻⁴⁰ documenting a role for both barrier and immune-related genes. Finally, there is considerable overlap between FA genetic loci and **genome-wide association study (GWAS)**-identified loci for AD,⁴¹ asthma,⁴² and AR⁴³ (Fig 1).⁴¹⁻⁴⁴ The considerable overlap between FA and AD supports the mechanisms for FA suggested by the atopic march.^{44,45}

FAMILIAL AGGREGATION AND HERITABILITY OF FA

The first documented report of **familial aggregation** of FA was in 1996 in a survey of 622 families with probands (ie, an index case with disease) of self-reported, suspected, and known peanut allergy (PA) in the United Kingdom.⁴⁶ PA prevalence was found to increase through successive generations: 0.1% in grandparents,

GLOSSARY

DUAL ALLERGEN EXPOSURE HYPOTHESIS: The theory that low-dose cutaneous exposure to food antigens during infancy promotes allergic sensitization, whereas high-dose oral exposure induces tolerance.

ATOPIC MARCH: A pattern of progression of allergic diseases starting from infancy and typically includes atopic dermatitis, food allergy, allergic rhinitis, and asthma.

PROBAND: The first affected individual that is identified and serves as the starting point for a genetic study of a family.

CONCORDANCE: The presence of a particular trait in both members of a pair of twins.

LINKAGE DISEQUILIBRIUM: Where alleles on different loci occur together more often than would occur by chance because of their physical proximity on a chromosome.

HAPLOTYPE: A set of alleles/variants present on an individual chromosome that tends to be inherited together.

LOCUS: A specific, fixed location of a particular gene on a chromosome.

The editors acknowledge Jared Travers, MD, PhD, for preparing the glossary. Additional glossary terms can be found in Box 1.

TABLE I. Genetic loci and genes associated with FA identified by GWASs, CGASs, and G × E interaction studies organized by functional categories

Functional categories	GWAS	CGAS	G × E
Skin barrier integrity	FLG-AS1 , ⁷ SERPINB7 SERPINB2 ⁷	FLG , ⁸⁻¹² SPINK ^{13,14}	FLG ¹⁵
Vascular and endothelial cell factors	ANGPT4 , ¹⁶ CHCHD3 EXOC4 , ¹⁶ CTNNA3 , ¹⁶ SKAP1 ¹⁶		
Innate immunity	HLA-DPB1 , ^{17,18} HLA-DRB1 , ¹⁷⁻¹⁹ IL26 , ¹⁷ MALT1 ²⁰	CD14 , ^{21,22} HLA-B , ²³ HLA-DPB1 , ²⁴ HLA-DRB1 , ²³⁻²⁵ MALT1 ²⁰ IL10 , ^{26,27} IL2 IL21 * KIAA1109 , ^{12,28} TLR10 / 6 * FAM114A1 , ²⁸ TSLP * WDR36 ¹²	
Adaptive immunity	C11orf30 LRRC32 * LOC101928813 , ^{7,16} HLA-DPB1 , ^{17,18} HLA-DQA1 , ¹⁷⁻¹⁹ HLA-DQA2 , ^{18,19} HLA-DQB1 , ^{7,17-19,29} HLA-DRA , ^{18,19} HLA-DRB1 , ¹⁷⁻¹⁹ HLA-DRB5 , ¹⁸ IL26 , ¹⁷ IL4 * KIF3A , ⁷ MALT1 ²⁰	C11ORF30 LRRC32 , ^{12,30} C-REL , ³¹ HLA-B , ²³ HLA-DPB1 , ²⁴ HLA-DQB1 , ^{23,24,32,33} HLA-DRB1 , ²³⁻²⁵ IL10 , ^{26,27} IL2 IL21 * KIAA1109 , ^{12,28} KIF3A IL13 , ^{12,34} STAT6 , ^{12,35} TSLP * WDR36 ¹²	MALT1 ²⁰
Immune modulation and regulation	IL26 , ¹⁷ IL4 * KIF3A , ⁷ SERPINB7 SERPINB2 ⁷	C-REL , ³¹ IL10 , ^{26,27} IL28B , ³⁶ IL2 IL21 * KIAA1109 , ^{12,28} KIF3A IL13 , ^{12,34} STAT6 ^{12,35}	DBP/GC ³⁷
Other	ADGB , ³⁸ ARHGAP24 , ¹⁶ ATP10A , ¹⁷ BCAS1 , ¹⁷ DLX2 ITGA6 , ¹⁶ FXR1 , ¹⁷ GNPDA1 NDFIP1 , ²⁰ GYG1P2 RNU6-67P , ³⁸ IER5L , ¹⁷ LINC00540 BASPI1 , ²⁰ LINC00298 LINC00299 , ²⁰ LINC01260 CKCN15-AS1 , ²⁰ LINC01568 LOC101928035 , ²⁰ LINGO2 , ¹⁷ LMX1A , ¹⁷ LOC101927166 , ¹⁶ LOC101927947 , ³⁸ MDN1 , ¹⁷ MMP12 MMP13 , ¹⁶ NAV2 , ¹⁷ PADI6 , ²⁰ PAFAH1B1 , ¹⁷ PAX2 , ¹⁷ PLAGL1 , ¹⁷ PLPP7 PRRC2B , ²⁰ PYROXD1 , ¹⁷ RCC2 ARHGEF10L , ²⁰ RGS21 , ¹⁷ RIMS2 , ¹⁷ RNF130 , ¹⁷ SALL3 , ¹⁷ SLC2A9 , ¹⁷ SORBS2 , ¹⁷ SV2C , ¹⁷ TES , ¹⁷ TRIM2 , ²⁰ ZNF652 ³⁸	CCDC80 , ¹² CLEC16A DEXT , ¹² GLB1 , ¹² NAT2 , ³⁹ NLRP3 , ⁴⁰ OR10A3 NLRP10 , ¹² OVOL1 , ¹² TMEM232 SLC25A46 , ¹² TNFRSF6B ZGPAT , ¹² ZNF365 , ¹² ZNF652 ¹²	

Genes/loci that are bolded are those that are replicated within the study, or have evidence across multiple studies. For genetic loci mapping to multiple genes, the index gene for each category is marked with an asterisk (*).

1.6% in parents, and 7% of siblings of the *proband*,⁴⁶ a pattern often noted in diseases with a genetic predisposition because closer relatives share more genetically.

Twins are a special category of sibling pairs where there is greater shared (early) environment in twins versus siblings. In addition, the genetics for monozygotic (MZ) versus dizygotic (DZ) twins differs, with 100% versus 50% shared genetics, respectively; the comparison of *concordance* (ie, both individuals within the twin pair have FA) between MZ and DZ twins provides insight into the role of genes versus environment. In 2000, a small twin study including 58 twin pairs from the United States showed much higher concordance of PA among MZ twins (64.3%) than among DZ twins (6.8%), with *heritability* estimates at 81.6%.⁴⁷ A study in a Chinese population including 826 twin pairs evaluated sensitization to 9 foods (milk, egg, wheat, peanut, soybean, sesame, walnut, shellfish, and fish), confirmed higher concordance in sensitization for any food in MZ (52.1%) than in DZ (39.2%) twins, and reported a heritability of FS of 56%.⁴⁸ Higher prevalence of PA in siblings of allergic children than the siblings of nonallergic/nonsensitized children (8.5% vs 1.3%) has also been noted in 514 families from Canada.⁴⁹ Siblings of peanut-allergic children had a 7-fold greater risk for PA, and interestingly birth order also appears to have an effect on risk, with younger siblings bearing the highest risk.⁴⁹ Elevated risk to siblings of peanut-allergic children was also noted in the Chicago Family Cohort Food Allergy study⁵⁰ including 581 nuclear families, with evidence for heritability in food sIgE (15%-35%).

The largest and most robust familial aggregation study including 5276 infants was performed in the HealthNuts study cohort in Australia.⁵¹ They used OFC to egg, peanut, or sesame allergy to define FA, and reported that the risk for FA in the children increased with increasing numbers of atopic family members. However, they found that the risk for FA in infants with 2 allergic family members compared with no allergic family members was lower in children with both parents born in Australia (odds ratio [OR], 2.2; 95% CI, 1.5-3.3) than in those with both parents born in Asia (OR, 4.7; 95% CI, 2.3-9.5). The reverse was noted for the risk for FA in infants with 1 allergic family member compared with no allergic family member, higher in children with both parents born in Australia (OR, 1.9; 95% CI, 1.3-2.7) than in Asia (OR, 1.4; 95% CI, 0.7-2.9). The overall lower rates of reported FA among parents born in East Asia, but higher rates among their infants, supports interactions with environmental factors. They also found that maternal history of eczema and asthma, and sibling history of AR were predictors of egg allergy (EA) in infants, whereas maternal and paternal histories of asthma with AR were predictors of PA in infants.⁵¹ Most recently, the Chicago Family Cohort Food Allergy study⁵² applied a set of clinical criteria to data gathered from the questionnaires, immunologic markers of sIgE measurements, and skin prick tests to 9 food allergens (egg white, sesame, peanut, soy, cow's milk, shrimp, walnut, cod fish, and wheat) and was able to dissect FA from FS. They reported that among siblings of children with FA, 53% siblings were food sensitized but did not have clinical FA, 33.4% had neither FS nor clinical FA, and only 13.6% were

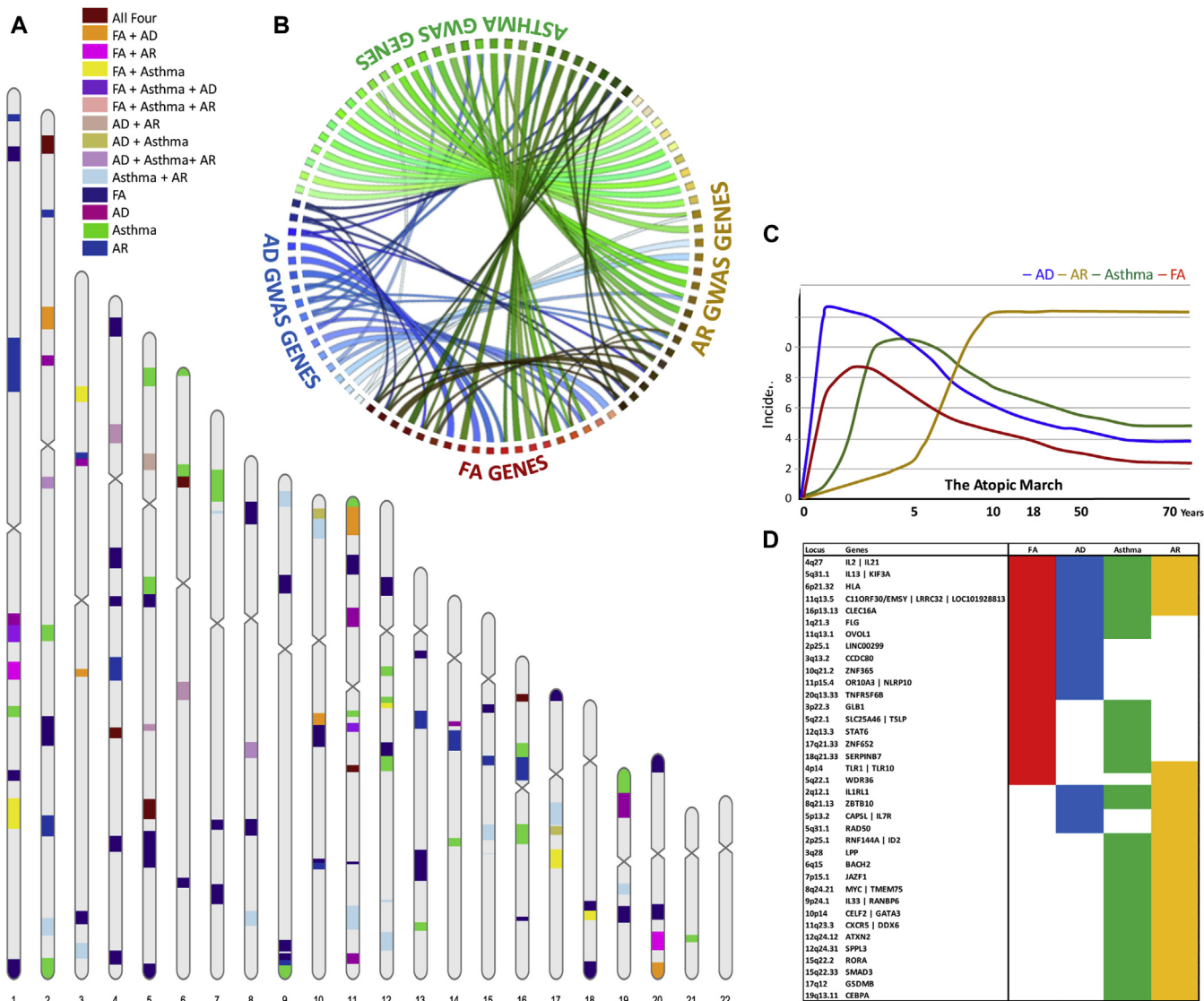


FIG 1. Overlap between FA-associated genes (from CGASs) and loci (from GWASs) and asthma, AD, and AR GWAS loci. **A**, Karyogram shows the genetic loci-associated FA from Table 1 and the largest GWAS-reported loci for AD,⁴¹ asthma,⁴² and AR.⁴³ The colors represent the overlap in chromosomal position between the 4 phenotypes of the atopic march. **B**, Circos plot showing connections between overlapping loci for the 4 phenotypes. FA loci show the highest overlap with AD loci as compared with asthma or AR GWAS loci. **C**, The proposed model for atopic march showing the development of FA, asthma, and AR correlates AD severity in early life, adapted from Davidson et al.⁴⁴ **D**, Shared genes among atopic march phenotypes presented in Fig 1, B.

both sensitized and had clinical FA; an overall higher prevalence in siblings was noted for FS versus FA.

These studies depict a wide range in the heritability estimates for FA and FS, ranging from 15% to 82%,^{47,48,50} and the risk to siblings in FA studies ranges from 1.3-fold to 12-fold.^{46,49,50,52} The Chicago Family Cohort Food Allergy study even noted that the observation of 1 in 8 siblings at risk of developing FA represented only a minimally higher risk than the risk in the general population (1 in 12) and concluded that FA in an index child is not an indication to test siblings.⁵² Although this wide spectrum of heritability estimates for FA and FS may seem contradictory at first, these are in fact not unexpected observations. FA is a disease with a strong environmental component; allergen exposure and its timing and route are key components to the

development of disease⁶ in addition to genetic susceptibility. The less-than-100% concordance in FA between MZ twins, but the higher concordance in MZ twins compared with DZ twins, offers the insight that there are genetic factors at play (MZ twins share their full genome, whereas DZ twins share only half), but there are certainly environmental factors at play as well (given that in <<100% of MZ twin pairs, both twins have FA). The wide range in heritability represents the relative differences between genetic and environmental variability in the specific sample being studied. Take for example a study sample in which every child is exposed versus one in which no child is exposed. Even if the genetics were identical, the dramatic difference in exposure rates will result in differing disease prevalence, and consequently wildly differing heritability estimates.

This complex interplay of genes and environment in FA is further compounded by the assessment of allergy and/or sensitization in these studies, which ranges from brief questionnaire data, to skin prick test and/or sIgE measures and OFCs. Nonetheless, the overall collection of studies would support the role of genetics and its interaction with environment in FA, and there has been success in identifying genetic determinants of FA as illustrated below.

CANDIDATE GENE ASSOCIATION STUDIES IN FA

Candidate gene association studies (CGASs) for FA have primarily focused on genes known to be associated with asthma, AD, and GWAS-identified FA genetic loci. A comprehensive overview of the study designs of the CGASs performed for FS, FA, and food-induced anaphylaxis (FIA) is illustrated in Table E1, and reiterates the stated challenges with small sample sizes and definition of disease outcome. Of the 27 CGAS-identified genes/loci (Table 1), *filaggrin (FLG)* and the set of HLA genes have some of the most robust evidence. Given the striking overlap in HLA genes from CGASs and GWASs, and the complexity of HLA associations at the allelic level, these genes are discussed in a separate section of this review.

Filaggrin (*FLG*) located in the epidermal differentiation complex (EDC) region on chromosome 1q21.3 encodes profilaggrin and plays a key role in epithelial barrier function in allergic skin disease,⁵³ with well-established associations with AD,⁵⁴ asthma,⁵⁴ and AR⁵⁵ and increased levels of certain food sIgEs, indicating FS.⁵⁵ Cutaneous exposure to foods through an impaired skin barrier is hypothesized as a route of FS, and the timing and balance of cutaneous exposure relative to oral exposure may result in FA,⁵⁶ making *FLG* a perfect biological candidate. Much attention has been devoted to a set of loss-of-function (LOF)/null mutations including R501X, 2282del4, R2447X, and S3247X mutations. The first evidence for *FLG* LOF mutations in PA was published almost a decade ago⁸ in PA cases confirmed with OFC compared with population-based control subjects from the United Kingdom, the Netherlands, and Ireland. Strong effect sizes (OR, 5.3; 95% CI, 2.8-10.2) were noted for a null genotype, and findings were replicated in a Canadian replication cohort albeit with weaker effects (OR, 1.9; 95% CI, 1.4-2.6). The Australian HealthNuts cohort⁹ confirmed the strong effects *FLG* has with FS (OR, 3.0; 95% CI, 1.0-8.7) and FA (OR, 2.9; 95% CI, 1.0-8.6) even after adjusting for any association with eczema. Importantly, no associations were observed with EA or PA within the egg-sensitized or peanut-sensitized infants, respectively,⁹ suggesting no role for allergy beyond sensitization. The relationship between *FLG* LOF mutations and PA was investigated in a Canadian cohort,¹⁰ and significant associations were observed (OR, 1.96; 95% CI, 1.49-2.58), which were confirmed to be independent of a history of asthma. In a longitudinal study exploring the time-order relationships between *FLG* LOF mutations and FA and FS¹¹ in children from the Isle of Wight birth cohort,⁵⁷ sustained effects were noted at younger (OR, 31.46; 95% CI, 2.86-100) and older ages (OR, 4.25; 95% CI, 1.55-11.61) for FA. They also reported that the effect of *FLG* LOF mutations on FA was an indirect effect through eczema and FS in the early ages.¹¹ There has been limited investigation into the role of *FLG* in FA beyond European ancestry populations, with only a single report confirming its role in Japanese subjects,¹² with significant associations noted for 6 *FLG* LOF variants and FA (OR,

1.63; 95% CI, 1.28-2.07). Two negative reports for *FLG* have been noted for cow's milk allergy (CMA).^{28,32} Taken together, *FLG* is perhaps the strongest candidate gene in FA aside from HLA genes. Although there does seem to be some conflict in whether *FLG* LOF mutations increase the risk of FS through impaired skin barrier function caused by filaggrin deficiency with¹¹ or without a further role in progression to FA,^{9,20} the cumulative evidence strongly supports the role of skin barrier function in FA.¹¹ Furthermore, the observation that the associations remain significant even after the adjustment for eczema would suggest an independent effect on FS⁹ beyond AD. Importantly, *FLG* associations seem to not have specificity for type of FA, but a more generalized effect for FS and FA. There is also a consistency of effect, with same *FLG* LOF mutations increasing the risk to phenotypes across the atopic march. The risk effects for *FLG* LOF mutations are strongest for AD (OR, 11.56; 95% CI, 5.73-24.74,⁵⁸), followed by FA (OR, 5.3; 95% CI, 2.8-10.2,⁸) and asthma (OR, 3.55; 95% CI, 1.87-7.02,⁵⁹); no associations have been reported for AR.

SPINK5 encodes lymphoepithelial Kazal-type-related inhibitor, which is involved in regulation of desquamation (shedding of outermost layer of epidermis).⁶⁰ The p.Glu420Lys polymorphism was found to increase the risk for FA in a Japanese AD cohort¹³ (OR, not reported [NR]), and associations of multiple single nucleotide polymorphisms (SNPs) have also been noted for FA in the Australian HealthNuts cohort¹⁴ including a multiethnic study sample of whites, Asians (South-East Asians), and Mixed Asian-whites (OR, 1.83-2.95; 95% CI, 1.11-1.95 to 3.03-5.83). Similar to *FLG*, these associations have strong effects (maximum OR, 2.95), and independence of eczema status,¹⁴ confirming the importance of an impaired skin barrier in FA.

STAT6 plays a central role in the production of IL-4 and IL-13 cytokines and in their signal transduction pathway for IgE class switching, an important component in allergic responses.⁶¹⁻⁶³ The first reported association was with nut allergy in a UK study³⁵ (OR, 3.9; 95% CI, 1.9-8.3), with documentation of a role for not just risk of nut (peanut and/or tree nut) allergy but also severity of the allergy.³⁵ Although negative reports do exist for the same *STAT6* genetic variants in a Japanese study, it was very small (66 controls/14 cases) and hampered by low power.⁶⁴ Evidence for the role of *STAT6* as a candidate gene extends beyond nut allergy. In a subgroup of the GENEVA cohort,⁶⁵ including Dutch children with FA defined by any positive double-blind placebo-controlled OFCs for PA and CMA, *STAT6* was found to be associated with PA (OR, NR), higher sIgE levels to peanuts and cow's milk, more severe symptoms for both peanut and cow's milk, and greater eliciting doses during the double-blind placebo-controlled OFC. These multiple studies document the role of *STAT6* in FA independent of allergenic food (ie, across multiple allergens), and equally important, they suggest a role in severity of the allergy beyond just risk.

CD14, a known asthma *locus*,⁶⁶ encodes a pattern recognition receptor CD14 that binds to LPSS, activating antigen-presenting cells with subsequent release of proinflammatory cytokines.⁶⁷ A promoter polymorphism (c.-159C>T) previously implicated for asthma was shown to be associated with FA in white subjects (OR, 1.7; 95% CI, 1.1-2.8)²¹ but not in a Japanese population.⁶⁸ Associations with CD14 variants have also been shown²² within a sibling-pair design, with predominantly European ancestry subjects for PA (OR, 1.97; 95% CI, 1.02-3.79) and peanut-specific

(ps) IgE.²² Interestingly, *CD14* is a gene with known G × E interactions with endotoxin exposure, and observed population differences given environmental exposures in high- and low-endotoxin environments,⁶⁹ which may help explain in part differential observations in FA between populations.

IL-10 and TGF-β1 are anti-inflammatory cytokines^{70,71} known to suppress allergen sIgE production. Interestingly, all CGASs on these anti-inflammatory cytokines have been in non-European ancestry populations. The association between FA and polymorphisms of *IL10* and *TGF-β1* genes was first investigated in Japanese children,²⁶ and the *IL10* c.-1082A>G SNP was found to convey an increased risk for the development of FA (OR, 2.4; 95% CI, 1.0-6.0).²⁶ In a study looking at IgE-mediated CMA in Brazilian children,²⁷ once again associations were observed only for *IL10*, with higher risk in a persistent subgroup (OR, 1.74; 95% CI, 1.14-2.81). In a small-scale study in a Taiwanese population (N < 100), although no associations were detected for allergy, the authors report significant associations with egg white sIgE.⁷²

A study in Australian children has reported the association between *IL-28B* gene and IgE-mediated FA.³⁶ *IL-28B* gene encodes cytokine IFN-λ3, a member of type III IFN family that has immunomodulatory functions. Despite the very limited sample size (30 cases with physician-diagnosed FA and 35 nonallergic controls of Caucasian ancestry), the authors were able to identify a nominal association for FA (OR, 3; 95% CI, 1.8-5.2); however, there has been no replication beyond this 1 study, and therefore evidence for *IL-28B* is less robust. IL-13 mediates IgE class switching necessary for the development of T_H2-mediated allergic immune response⁷³ and has been extensively studied in the context of asthma,⁷⁴ AD,⁷⁵ and AR.⁷⁶ *IL-13* variants were associated with challenge-proven FA (OR, 1.75; 95% CI, 1.20-2.53) to a greater degree than FS (OR, 1.48; 95% CI, 0.98-2.23) in the Australian HealthNuts cohort,¹⁴ along with association for plasma total IgE levels. Although this is the only CGAS on *IL-13*, the discoveries were replicated in an independent replication cohort within this single report.³⁴

Gawronska-Szklarz et al³⁹ studied the alleles in *NAT2*, which encodes the *N*-acetyltransferase 2 enzyme that participates in the detoxication of many drugs and arylamine xenobiotics. Polymorphisms in *NAT2* result in slow and fast acetylation phenotypes, and studies have reported a dominance of slow acetylation activity in allergic^{77,78} and atopic patients.⁷⁹ This study found that the risk of developing FA was almost 3 times higher in slow acetylators than in controls (OR, 2.8; 95% CI, 1.6-4.9). Although this is a single CGAS on *NAT2*, it is backed up by the orthogonal evidence from previous studies connecting slow acetylation with allergic phenotypes, and together supports the role for acetylation genotypes as factors of individual susceptibility to FA.³⁹

NLRP3 encodes pyrin protein, which controls the activity of inflammatory caspase-1 by forming complexes called inflammasomes⁸⁰ and has been associated with autoimmune inflammatory diseases and Crohn disease.⁸¹ A study in a Japanese population assessed the association of *NLRP3* polymorphisms with susceptibility to FA and FIA,⁴⁰ a life-threatening condition that can lead to various cutaneous, respiratory, gastrointestinal, and cardiovascular symptoms including hypotension, vascular collapse, and cardiac dysrhythmia. Although no significant associations were observed for FA, significant associations were noted with FIA (OR, 1.53-1.81; 95% CI, 1.09-1.27 to 2.16-2.56), and the risk

alleles were found to increase the enhancer activity of *NLRP3* expression, and increase *NLRP3* mRNA stability.⁴⁰ In a case-control study of 30 Algerian cases with IgE-mediated CMA and 28 nonallergic controls,³¹ an SNP in *C-Rel* was found to be associated with CMA (OR, 4.11; 95% CI, 1.82-9.29). *C-Rel* encodes transcription factor c-REL, a subunit of nuclear factor kappa B transcription factor, and has been implicated in inflammatory diseases such as ulcerative colitis⁸² and celiac disease.⁸³

There have been CGASs examining biological candidates with negative results for *FcγRIIa*,⁸⁴ Toll-like receptors (TLRs, *TLR-2*, and *TLR-4*),⁸⁵ *FOXP3*,³¹ and 2 closely related genes, *IDO1* and *IDO2*.⁸⁶ It should be noted that all these studies may have been severely underpowered (sample sizes <200), making the exclusion of these candidate genes for FA somewhat difficult. Finally, although these FA CGASs typically focus on 1 or 2 biological candidate genes, some studies have targeted GWAS-identified loci as the set of candidate genes. Using this parallel approach, associations with CMA have been documented for *TLR10/1/6* and *IL2*,²⁸ with FA for *C11orf30/LRRC32*, *TMEM232/SLC25A46*, *TNFRSF6B/ZGPAT*, *OVOL1*, *KIF3A/IL13*, *GLB1*, *CCDC80*, *ZNF365*, *OR10A3/NLRP10*, *IL2/IL21*, *CLEC16A/DECI*, *ZNF652*, *TSLP/WDR36*, and *STAT6*,¹² and with FA for *C11orf30/LRRC32*.³⁰

An examination of the broad functional categories of these CGAS-identified genes offers support to the Dual Allergen Exposure hypothesis on the pathophysiology of FA, with a prominent role for barrier and immunity-related genes. A disrupted skin barrier may facilitate cutaneous exposure to food allergens, and immunologic processes mediated by immune-related molecules during sensitization may lead to the progression to FA subsequent to sensitization. In fact, the genes identified through the CGAS for FA can be broadly classified into 4 functional categories described in Table I: (1) genes playing roles in skin barrier integrity; (2) genes associated with innate immunity; (3) genes associated with adaptive immunity; and (4) immunoregulatory and immunomodulatory genes. These candidate genes often have more than 1 study with direct genetic evidence, or some orthogonal evidence from nongenetic data (see Table E2 in this article's Online Repository at www.jacionline.org). The CGAS approach is limited in that it does not have the capacity to identify novel genes that may add to our understanding of the pathophysiology of FA because each gene is selected on the basis of previous knowledge. However, the advantage to this approach is that it is narrow in hypothesis and not limited by the stringent thresholds set in place with association testing in the genome-wide approaches described below.

GWASs OF FA

The unbiased GWAS approach takes advantage of the genetic architecture of human populations wherein SNPs are often found within blocks of *linkage disequilibrium* (LD, ie, where all SNPs within a block are highly correlated to each other). GWAS measures a reduced set of SNPs that can be used as a proxy for all remaining variants within the block. Importantly, the foundation for the GWAS approach is the “common disease, common variant” hypothesis, wherein common diseases are hypothesized to be attributable to many common genetic variants.^{87,88} It is important to point out that the GWAS approach does not in fact implicate genes (unlike the CGAS above), but rather identifies genetic loci, and relies on *fine-mapping* (Box 1) follow-up approaches

to hone in on causal genetic variants and specific genes within the loci. With no studies devoted to fine-mapping FA genetic loci, the assignment of loci to genes by GWASs is driven by physical proximity of genes to the region of association for the summaries below.

There have been 8 GWASs of FA (Table I; see Table E3 in this article's Online Repository at www.jacionline.org) and overall, these highlight 4 points: (1) As expected, GWAS loci are generally common in frequency. (2) They have modest effect sizes on average (ORs, <1.5). (3) The single most replicated region maps to the HLA region and HLA class II genes (*HLA-DR/DQ*). (4) With the exception of *HLA* and *FLG*, there is no overlap in genes identified from the CGAS and GWAS approaches. As with CGAS, there is a great degree of variability in the definition of FA in the GWASs, and therefore difficulty in our ability to truly disentangle FA from FS, on the basis of ascertainment of cases and unaffected controls across these studies as outlined in Table E1. In fact, with some studies using unphenotyped population-based controls, we may also be limited in discerning FA genes from general atopy genes. There is also variability in definitions of GWAS thresholds, and for the purposes of this review we report all loci meeting at least a suggestive threshold defined by the authors (Table E3), but only summarize in detail those that pass the stronger, standard GWAS threshold ($P < 5 \times 10^{-8}$) below. Unlike CGASs, CIs are not often reported for GWASs, and therefore not presented in this section.

The first GWAS locus for FA implicated the HLA region in the US-based Chicago Family Cohort Food Allergy Study¹⁹ where they performed GWASs for any FA among 9 foods (Table E1) and the 3 most common types of FA individually (peanut, egg white, and cow's milk). No genome-wide significant associations were found for FA overall, EA, or CMA. Only 1 GWAS signal was identified for PA, mapping to HLA class II genes. Two identified SNPs rs9275596 (OR, 1.7, mapping to an intergenic region between *HLA-DQB1* and *HLA-DQA2* genes) and rs7192 (OR, 1.7, a p.Leu242Val change in *HLA-DRA*) were highly correlated and represent a single risk factor for PA. In an extended approach looking at maternal effects, which serves as a proxy for the genetic interaction with the intrauterine environment,³⁸ significant maternal effects were noted with FA at rs4235235 (relative risk, RR, 0.36; $P = 4.82 \times 10^{-8}$) located in a noncoding RNA gene *LOC101927947*. However, no maternal effects were detected for PA, EA, or CMA.

The second GWAS of FA was done on challenge-proven pediatric PA cases and controls from the HealthNuts cohort.¹⁷ Despite a small sample size (73 PA cases and 148 nonallergic controls), this multiethnic GWAS including European, Mixed (European/Asian), and Asian ancestries was able to identify a locus (rs10018666, OR, 5.86) mapping to the *SLC2A9* gene reaching genome-wide significance but the authors were unable to replicate this finding.

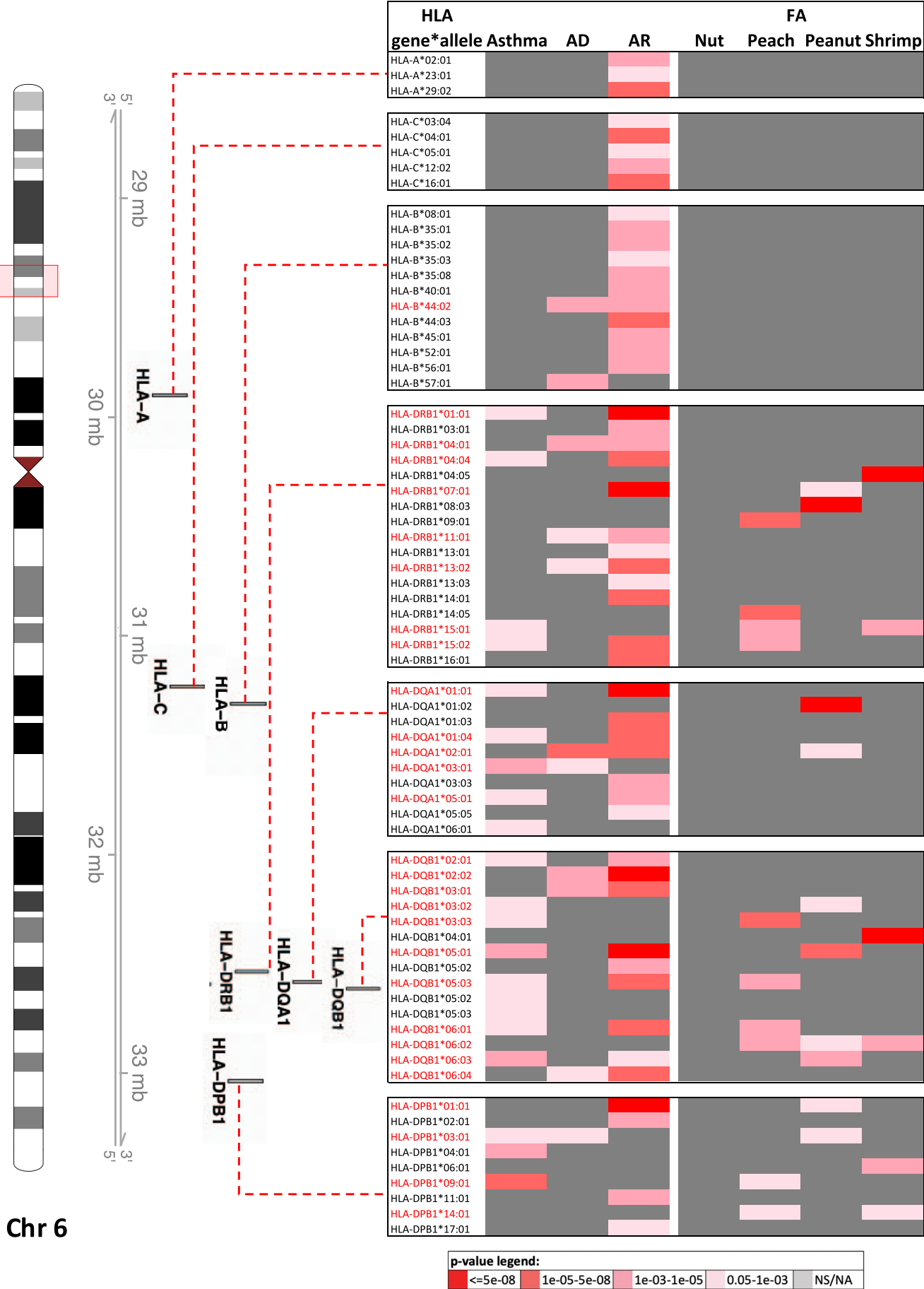
The European-based Genetics of Food Allergy (GOFA) study⁷ identified 2 loci associated with FA. The first of these mapped to the EDC (rs12123821, OR, 2.55) near the *FLG* gene and the second to the cytokine gene cluster (rs11949166, OR, 0.60) on chromosome 5. Both loci had robust replication in the Chicago Family Cohort Food Allergy study. Given that both the EDC and cytokine gene cluster region are known AD loci, they were specifically examined for their independent effects on FA, and both were found to retain independent effects of FA risk beyond AD. Combining the GOFA and Chicago Family Cohort Food

Allergy Study revealed 2 additional FA susceptibility loci. The peak SNP on chromosome 11 (rs2212434, OR, 1.29) is an intergenic variant between *C11orf30* and *LRRC32* genes that reached genome-wide significance for FA, but not any specific FA. The peak SNP on chromosome 18 (rs12964116, OR, 1.90) is located in intron 1 of *SERPINB* and reached genome-wide significance for FA and was also associated with PA. A second SNP mapping to *SERPINB* (rs1243064, OR, 1.65) was found for EA. This study was the second GWAS to map the HLA locus with a 3' untranslated region (UTR) variant in *HLA-DQB1* gene (rs9273440, OR, 0.66), showing association with PA, but not with other specific foods or FA in general.

A more recent study by Asai et al¹⁶ combined PA cases from the Canadian Peanut Allergy Registry study with controls from the Busselton Health Study in Australia in a discovery analysis. An additional 6 cohorts were included in 2 approaches: (i) as replication data sets to follow up on the discovery results in the Canadian Peanut Allergy Registry study and (ii) full meta-analysis framework including the (1) Chicago Food Allergy study, (2) Genetic Epidemiology Research on Aging study, (3) HealthNuts study, (4) German Understanding Food Allergy (UFA) study, (5) Dutch IDEAL study, and (6) Dutch GENEVA study. This meta-analysis reflects the single largest GWAS approach with approximately 36,000 samples. From the discovery/replication approach for PA, a locus (rs115218289, OR, 0.18) mapping to the *ITGA6* gene was identified to be associated with PA. This was also the third GWAS to identify that SNPs mapping to the HLA region determine the risk for PA (OR, 0.51-2.11). The HLA SNPs identified in the discovery analysis were found to have a trend with reaction severity of PA, specificity to PA, and independence from asthma comorbidity.²⁹

In the only GWAS focused entirely in a non-European ancestry population, Khor et al¹⁸ studied self-reported FA to 7 foods (kiwi, peach, Chinese yam, eggs, mackerel, crab, and shrimp) in 11,011 adult Japanese women from the Luna Luna cohort. Once again, the HLA region was the most strongly associated; in fact, it was the only GWAS signal for peach (rs28359885, OR, 1.80) and shrimp (rs74995702, OR, 1.9). Although both foods had peak associations mapping to HLA, they are distinct, independent signals from each other, supporting the role of allergen specificity of the HLA region for FA. Although this study is the largest single-study GWAS analysis, it should be noted that this is based entirely on a health questionnaire, and has limitations in its robustness of FA definition, and an inability to appropriately classify FS from FA.

The most recent GWAS of PA²⁰ tested for genetic determinants of PA in the Learning Early About Peanut Allergy (LEAP) study, and was the only GWAS to "control" for environmental exposure by limiting the GWAS to only the children randomized to the peanut avoidance arm. Using whole genome sequencing (WGS), they identified a genome-wide significant association signal on chromosome 18q21.32 mapping to the *MALT1* gene, with strong regulatory signatures for *MALT1* gene expression. The *MALT1* gene functions as a critical part of the CARMA1-BCL10-MALT1 complex, causing nuclear factor kappa B activation in B and T cells in response to antigen binding to their receptors, and plays a crucial role for both innate and adaptive immune responses.⁸⁹ Next to the strong reported effect sizes for *FLG* as summarized in the CGAS section, this association with *MALT1* was double in its effect size (OR, 10.99, with 58.6% of carriers developing PA in contrast to 12.7% of noncarriers). Importantly, the authors provide evidence



supporting its role as a genetic risk factor for progression to PA following sensitization. *MALTI* has not been implicated in previous genetic studies, and the study was unable to identify *FLG* or *HLA* as determinants of PA despite strong previous evidence for these genes from CGASs and GWASs. One of the key features of the LEAP study is its ascertainment criteria; the inclusion of peanut-sensitized participants at baseline facilitated the ability to test specifically for the risk of PA (beyond sensitization). This is in contrast to previous GWASs that may very well represent risk of sensitization and not specifically allergy.

Overall, the GWAS approach for FA has demonstrated convincing evidence for the CGAS-documented HLA locus albeit with modest effect sizes (OR, 0.47-2.11). In contrast, *FLG*, one of the strongest candidate genes, does not have much support from the larger GWAS despite its large effect sizes from CGAS (OR, 1.63-5.3; $P = 0.04-5.12 \times 10^{-7}$), with the exception of the EDC locus in the GOFA GWAS.⁷ This is potentially because the LOF mutations are not available on the array used, the association did not meet traditional GWAS thresholds and were not reported within the GWAS framework, or the nature of the unphenotyped population-based controls in GOFA. Despite the successes, the cumulative heritability in FA explained by these GWAS loci is limited; the 5 genome-wide significant loci identified by Marenholz et al⁷ account for less than 50% of heritability estimated from whole-genome data, suggesting other loci beyond these discoveries. A limitation with the GWAS approach is that the SNPs identified from the GWAS may not be the true causal variants themselves but generally a proxy for some unmeasured disease-causing variant that needs additional follow-up for discovery, and thus far there has been very limited follow-up of these loci. These GWASs have been plagued with small sample sizes, and heterogeneity in case definition similar to that described for the CGAS. In fact, the only attempted meta-analysis revealed sensitivity to FA definition criteria where the inclusion of studies with questionnaire-only diagnosis weakened results.¹⁶ Finally, and perhaps most important in the case of FA, these GWASs have all ignored $G \times E$ interactions with the exception of the most recent study in LEAP, and for a disease model in which heterogeneity in exposure leads to heterogeneity in disease outcome, this could be an added limitation in power and the reason for limited results from the GWAS of FA, and residual unexplained heritability.

In addition to the 4 functional categories largely captured within the CGAS approach, the FA-associated genes/loci identified through the unbiased GWAS approach point out one functional category of vascular and endothelial cell factors (Table I). Genes related to vascular and endothelial cell factors could be involved in the pathophysiology of FA through 2 putative mechanisms: (1) an endothelial barrier defect promoting sensitization, and (2) endothelial cells acting as antigen-presenting cells. In fact, across the landscape of FA genetic loci identified from both the GWAS and CGAS approaches, there is a marked enrichment for both adaptive and innate immunity

pathways (see Fig E1 in this article's Online Repository at www.jacionline.org).

HLA GENES AND FA

The MHC lies on chromosome 6p21.3, and is rich in immune-response genes, including the *HLA* genes, which encode families of cell-surface proteins that function as key determinants of antigen recognition by the adaptive immune system. Despite the HLA region being associated with more diseases than any other region of the genome,⁹⁰ particularly with immune, infectious, and allergic diseases, it has been challenging to dissect its role in disease etiology. This is due in part to extremely high levels of genomic polymorphism (referred to as alleles) at several of these loci (eg, the class I *HLA*-A, -B, and -C genes, and the class II *-DRB1*, *-DQB1*, *-DQA1*, *-DPB1*, and *-DPA1* genes) and strong linkage disequilibrium (LD) across the region. There are more than 26,000 alleles at the *HLA* genes identified to date,⁹¹ most of which are within the peptide-binding groove of the HLA molecule or in the region that interacts with the T-cell receptor.⁹² The result is a diverse array of HLA molecules that selectively bind peptides derived from degraded proteins in a process known as antigen presentation. T lymphocytes that contain clonally restricted receptors for these peptide-HLA ligands undergo a differentiation and maturation cascade upon binding that ultimately determines whether the resulting immune response is inflammatory, regulatory, or—as is often the case—both. Depending on the particular peptide-HLA combination and on tissue microenvironmental cues, such as concurrent cytokine recognition, these T-cell responses can direct B lymphocytes (a process known as “T-cell help”) to produce antigen-specific immunoglobulins of various isotypes, such as the IgE molecules that have critical effector functions in allergy. This sequence of events offers several steps in which genetic polymorphisms within *HLA* genes may influence allergic outcomes, including binding of specific peptides to HLA molecules, initial recognition or lack of recognition of particular allergens, the type of initial T-cell response,^{93,94} the balance between regulatory and helper T cells,^{95,96} and interactions between T and B cells that influence immunoglobulin isotype production.^{97,98}

For FA, the HLA locus is by far the strongest evidence from the GWAS, but as noted above, these GWAS associations are at the *locus* level and not at the *gene* level. Given the importance of HLA in antigen presentation, and the extensive work looking specifically at HLA alleles, we provide a detailed overview of the associations at the allelic level with FA in this section (see Table E4 in this article's Online Repository at www.jacionline.org). Because only some studies report CIs, we summarize only ORs in this section. HLA nomenclature is a standardized process,⁹¹ but it has changed over the course of the available publications for phenotypes in the atopic march. To simplify interpretation, we report only those results where the HLA allele has up to 2 digits resolution (sets of digits separated by a colon ‘:’). The digits before the

FIG 2. HLA risk alleles associated with asthma,⁹⁹ AD,¹⁰⁰ AR,⁴³ and 4 different food allergens. Red box on the ideogram of chromosome 6 highlights the HLA region in the human genome. The association between 4-digit alleles of 3 HLA class I genes (*HLA*-A, -B, and -C), and 4 HLA class II genes (*HLA*-DQA1, *DQB1*, *DRB1*, and *DPB1*) and the atopic phenotypes is presented. Alleles of HLA class II genes are associated with all phenotypes, whereas alleles of class I genes are largely associated with AR.

first colon (eg, *HLA-DQA1**01) reference the serological antigen type, and the next set of digits (eg, *HLA-DQA1**01:02) is the subtype. Alleles whose numbers differ in the 2 sets of digits differ in 1 or more nucleotide substitutions that change the amino acid sequence of the encoded protein. The HLA region is also widely implicated across the atopic march (Fig 1); therefore, we provide a contrast of these associations at the allelic level for FA and across other atopic march phenotypes (asthma,⁹⁹ AD,¹⁰⁰ and AR⁴³) in Fig 2.^{43,99,100}

In the first report on HLA alleles, Boehncke et al¹⁰¹ compared FA cases with pollinosis to healthy controls. They tested for association with 8 food allergens and reported that patients with the *HLA-DRB1**08 allele had a high risk of PA (RR, 6.04). In a family-based cohort, Howell et al²⁴ reported an increased risk for PA for *DRB1**08 (OR, 4.37) and *DQB1**04 (OR, 6.79). In 2006, Shreffler et al¹⁰² studied sibling pairs for 7 HLA-DQ and 18 HLA-DR alleles, and reported nominal associations between PA and DQ7 (*03:01, *03:04, *03:05, *03:09, *03:10, *03:12, and *03:13, ORs, NR). In a study of peanut-allergic subjects and their peanut-tolerant full siblings, Dreskin et al²⁵ looked at how differences in levels of pIgE and pIgG might be related to differences in the ability to present peanut allergens in a thorough evaluation of 59 HLA class II alleles of *HLA-DRB1*, *HLA-DQB1*, and *HLA-DPB1* genes. No associations were noted between pIgG and pIgE levels and HLA class II alleles. However, it is highly likely that the quantitative level of pIgE and pIgG₄ is a function of G × E interaction between exposure to peanut antigen and the specific HLA alleles that are involved in the presentation of peanut peptides. Therefore, this negative finding has major limitations because interactions with exposure were not considered.

The largest CGAS study on HLA was performed by Madore et al.³³ They found associations between PA and 5 *HLA-DQB1* alleles. *DQB1**02 (OR, 0.12), *DQB1**03:02 (OR, 0.52), *DQB1**05 (OR, 0.21), and *DQB1**05:01 (OR, 0.25) alleles were protective, and *DQB1**06:03 (OR, 2.59) was a risk allele for PA. Given that *HLA-DQB1* gene is also a susceptibility gene for asthma, they adjusted their analysis for asthma, and 2 alleles *DQB1**02 (OR, 0.09) and *DQB1**06:03 (OR, 2.82) continued to show their association with PA. HLA associations are not limited to PA; nominal associations have also been observed for HLA-B*07 and HLA-*DRB1**11 for nut-allergic patients compared with atopic controls, and HLA-*DRB1**13 and HLA-*DQB1**06 comparing patients to blood donor controls.²³ HLA class II haplotypes carrying HLA II alleles *DQB1**06:02 and *DQB1**05:01 were also found to modulate antibody responses to CM proteins,³² revealing both risk and protective alleles at *DQB1* for CMA-related traits.

With the availability of bioinformatic approaches to leverage SNP GWAS data to impute HLA alleles,¹⁰³⁻¹⁰⁵ several of the GWASs have used this approach to look beyond the SNPs (described in the GWAS review above) to examine specific HLA alleles with FA risk. In the first GWAS of FA, 50 HLA class II alleles were analyzed for PA in a European ancestry population.¹⁹ They identified 2 alleles (HLA-*DQA1**01:02, OR, NR, and HLA-*DQB1**06, OR, NR) as risk alleles for PA. In the second GWAS of PA, Martino et al¹⁷ performed an in-depth exploration of HLA alleles for PA. Although no result reached genome-wide significance for PA, they were able to replicate both these findings (HLA-*DQA1**01:02, OR, 1.81, and HLA-*DQB1**06, OR, 2.26) reported by Hong et al¹⁹ with similar directions of effect. HLA alleles have also been examined for peach and shrimp allergies.¹⁸

HLA-DRB1 (*09:01, *14:05, *15:01, and *15:02), *HLA-DQB1* (*03:03, *06:02, *05:03, and *06:01), and *HLA-DPB1* (*14:01 and *09:01) were all found to increase the risk for peach allergy (OR, 1.4-2.5; Table E4). For shrimp allergy, *HLA-DRB1* (*04:05 and *15:01), *HLA-DQB1* (*04:01 and *06:02), and *HLA-DPB1* (*06:01 and *14:01) were found to increase the risk (OR, 1.55-5.24; Table E4). It is important to note that the alleles for the 2 foods are different from each other, and also different from HLA-*DQA1**01:02 identified for PA, reflecting a specificity for allergen.

It is challenging to dissect independence between the associations from the GWAS SNPs and the HLA alleles/haplotypes, limiting our ability to test whether there are quantitative (SNPs identified are often strong regulatory SNPs for HLA gene expression across multiple HLA genes) or qualitative (alleles representing binding of specific allergenic peptides forming ligands for specific T-cell recognition) effects or both. Notably, extensive LD within the HLA region results in the cosegregation of combinations of HLA allelic variants at multiple loci. Indeed, several of the frequent allergy-associated HLA alleles mentioned above, such as *DQB1**06:02 and *DQA1**01:02, coexist on a single **haplotype** together with particular *DRB1* and *DRB5* alleles, raising the additional question whether a single gene or a combination of these genes is driving the association with allergy. Nonetheless, the summary in Figure 2 highlights the following key features of HLA associations across phenotypes in the atopic march: (1) *HLA-DR/DQ* associations have consistent effects on FA when it comes to the atopic march. Often, the alleles are associated with 1 but not multiple phenotypes within the atopic march, and unlike *FLG* where the same LOF alleles convey risk across the atopic march phenotypes, here the specific HLA associations with FAs are often distinct from those with asthma⁹⁹ and AD.¹⁰⁰ (2) Even within FA, HLA allelic associations often differ between the specific allergen; for example, the HLA-*DQA1**01:02 is noted specifically for peanut and no other FA or atopic march phenotype. Although for many of the HLA alleles, associations across phenotypes of the atopic march are unique, alleles at the *HLA-DQB1* gene tend to be shared between atopic asthma and FA. Although some part of this could be reflective of tight LD with noncoding regulatory variants described above, we acknowledge that some part of this may also reflect cross-reactivity across allergens manifesting as associations noted across allergic phenotypes.

G × E INTERACTIONS IN FA

The role of environmental factors as key determinants of FA risk has been well established.¹⁰⁶ Many of these environment factors are thought to impact the development and regulation of the immune system either directly or indirectly. However, there is very limited understanding of how these factors affect the development of FA in the context of genetics. Despite the importance of the environment in FA risk, and the need to consider G × E interaction in a systematic fashion, very few such studies have been conducted to date.

Brough et al¹⁵ tested the hypothesis that early-life environmental peanut exposure may be a risk for PA development, and tested whether this relationship was affected by *FLG* LOF mutations in European children from the Manchester Asthma and Allergy Study. In carriers of *FLG* LOF mutations, there was a dose-response relationship between early-life environmental

exposure to peanut protein in household dust and subsequent peanut sensitization and PA. Each 2.7-fold increase in house dust peanut exposure during infancy was associated with a more than 6-fold increase in the odds of peanut sensitization and a 3.3-fold increase in the odds of PA. Koplin et al³⁷ tested whether polymorphisms in the *DBP/GC* gene that lower the vitamin D-binding proteins of the offspring could compensate for adverse effects of low serum vitamin D on FA risk at age 1 and 2 years from the HealthNuts study. The results from the study showed that low 25[OH]D3 serum levels (OR, 6; 95% CI, 0.9-38.9) and high vitamin D levels (OR, 4; 95% CI, 1.3-12.9) of the children were associated with FA only in participants with the GG genotype at the rs7041 SNP at age 1 year. The relationship between maternal use of vitamin D supplements during pregnancy and FA risk was also modified by the variant, with a significantly reduced risk of FA in infants with the GT/TT genotype (OR, 0.1; 95% CI, 0.03-0.41; $P = .001$) but not those with the GG genotype (OR, 0.34; 95% CI, 0.04-2.79; $P = .32$). In contrast, associations between infant formula use with added vitamin D and FA was not modified by genotype. They also found that vitamin D insufficiency at 2 years was associated with persistent EA (OR, 12.96) among infants with the GG genotype.

The only GWAS allowing for an unbiased genome-wide evaluation of $G \times E$ effects on PA is the LEAP study.²⁰ The setting of the clinical trial with high-risk participants randomized to peanut exposure or avoidance allowed for a stratified GWAS approach, and a strong $G \times E$ interaction is noted for the *MALTI* risk allele for PA when analysis was extended to quantitative psIgE levels across the full set of consumers and avoiders as described above.²⁰

GENETICS OF EOSINOPHILIC ESOPHAGITIS

Eosinophilic esophagitis (EoE) is a chronic inflammatory condition characterized by esophageal eosinophilia and dysphagia.¹⁰⁷ The food-related inflammation during EoE pathogenesis is classified as a mixed immune reaction,⁶ that is, both IgE- and cell-mediated immune responses. Candidate gene-based studies of EoE have shown that *CCL26*¹⁰⁸ and *FLG*¹⁰⁹ are associated with disease susceptibility, and several loci including *TSLP|WDR36*,¹¹⁰ *CAPN14*,^{111,112} *C11orf30|LRRC32*,¹¹² *STAT6*,¹¹² *ANKRD27*,¹¹² and *CLEC16A*¹¹³ have been identified through GWAS. Interestingly, genetic analysis study of EoE based on Immunochip platform found lack of association of EoE with the genetic variants in the HLA region genes.¹¹³ Although there are dissimilarities between immune reactions occurring during FA and EoE pathogenesis, there are overlapping genes and genetic loci (*C11orf30|LRRC32*,^{7,12,16,30} *CLEC16A|DEXT*,¹² *FLG*,⁸⁻¹² *STAT6*,^{12,35,65} *TSLP|WDR36*¹²) between the 2 that may suggest partly overlapping mechanism. For example, given similarities in the mucosal structure of the skin and the esophagus,¹¹⁴ disrupted barrier integrity due to *FLG* LOF mutations in the skin may cause cutaneous exposure to food allergen leading to FA, and in the esophagus may cause allergen-induced eosinophilic infiltration resulting in EoE.

CONCLUDING REMARKS

This review systematically collates the genetic association studies of FA where we have compiled the list of genetic loci, genes, and specific variants that show associations with FA and FS. It is useful to summarize these observations in

the context of the RR to sibs (λ_s), which for monogenic diseases or largely genetic disorders tends to be high (eg, $\lambda_s \sim 500$ for cystic fibrosis), but for FA is 1.3-fold to 12 with a complex interplay between environment and genes—a far more daunting challenge for discovery. Although the reviewed studies are plagued by low power, heterogeneity in definition of FA, variability in the comparison control group, and difficulty in our ability to truly disentangle FA from FS and general atopy genetics, they have no doubt led to a set of loci, genes, and variants that explain the risk for FA in part. With respect to the biological mechanism in FA, the genetic loci point strongly to the critical role of barrier and immune function both at individual gene levels (Table 1) and at pathway-based levels (Fig E1). In fact, the largest reported genetic effects on FA are from *MALTI* (OR, 10.99), *FLG* LOF (average OR, 2.9), and HLA alleles (average OR, 2.03), pointing to immune- and barrier-related mechanism. Taken together with the striking overlap between FA genetics and AD, asthma, and AR genetics, these loci offer collective support of previous hypotheses such as the atopic march and the Dual Allergen Exposure hypothesis. Despite these successes, the greatest challenge in the field of FA genetics is to elucidate the effect of the associated variant on expression, regulation, and function of associated gene(s) and to better understand the specific mechanism of action on FA risk and pathogenesis. The integration of genetic studies with other omics studies such as transcriptomics, proteomics, and metabolomics hold great promise in understanding the mechanism as discussed in our companion review,¹¹⁵ and this needs to be considered within study designs that better define outcome, enable the dissection of FA from FS, distinguish FA genetics from general atopy genes, and most importantly consider environmental interactions.

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Supplementary Table E1: Summary of genetic studies of food allergy.

Study Type	Cohorts	Study Design	Sample (N)	Ancestry	Phenotype	Phenotype Definition		Reference
						Cases	Controls	
CGAS		Cases, related controls and unrelated controls	454	Caucasian (British)	Peanut Allergy	Convincing history of allergic reaction and positive SPT to peanuts	Related controls == Non peanut allergic siblings (atopic + non-atopic); Unrelated controls == Population based cohort for bone marrow and cadaveric renal donors	Howell et al 1998 (102)
		Case Control	259	Caucasian (Polish)	Food Allergy (cow's milk, egg white, wheat flour, rye flour, soybean, codfish, pork, beef, chicken, chocolate, tomato, nuts including peanuts, celery, orange, kiwi)	Positive open controlled food challenge tests, positive skin prick tests, and increased blood serum level of specific IgE	Population based controls with no history of allergy and respiratory tract infections.	Gawron'ska-Szklarz et al 2001 (63)
		Case Control	300	Caucasian (British)	Nut Allergy (peanut, cashew, brazil nut, pecan, almond, hazelnut or walnut)	Positive SPT to peanut, cashew, brazil nut, pecan, almond, hazelnut or walnut	Atopic controls with a history of eczema, asthma or hay fever + Healthy controls with no information regarding atopic status	Amoli et al 2002 (40)
		Case Control	80	Japanese	Food Allergy	Diagnosis based on recognition of typical manifestations and the patient's history, with regard to the reproducibility of the reaction, the timing of the reaction, and response to elimination of particular foods from the diet. All FA patients had a positive RAST response to food to which they were susceptible.	Non atopic controls	Tamura et al 2003 (41)
		Case Control	138	European American, African American & Other	Food Allergy	History of an immediate reaction to a food and positive antigen test responses (SPTs or RASTs).	Non atopic, Non asthmatic controls	Woo et al 2003 (45)
		Case Control	1964	Caucasian (British), Mixed	Nuts Allergy (Peanuts, brazil nut, hazel nut, walnut, cashew, almond & pecan)	Evaluation of questionnaire by clinician, SPTs to nuts	Atopic control group == Atopy defined by a clinical history and positive SPT to at least two common allergens + Population based control group == random blood donors	Hand et al 2004 (106)
		Case Control	341	Caucasian (Polish)	Food Allergy (cow's milk, egg white, wheat flour, rye flour, soybean, codfish, pork, beef, chicken, chocolate, tomato, nuts including peanuts, celery, orange, kiwi)	Positive open controlled food challenge tests, positive SPTs and increased blood serum level of specific IgE to specific food allergens.	Healthy controls with no personal or family history of allergic background.	Pawlik et al 2004 (70)
		Case Only	117	Japanese	Food Allergy	An episode of immediate allergic reaction (skin, oral, respiratory, and/or gastrointestinal symptoms) within 1 hour of eating an allergenic food and was confirmed by positive CAP-RAST results.	--	Kusunoki et al 2005 (35)
		Case Control	146	Caucasians & Asians	Peanut Allergy	Recent acute clinical reaction with urticaria, angioedema, wheezing to ingestion of peanuts or a remote history of an acute reaction and a current elevated psIgE level ≥ 15 kIU/L.	Atopic and non atopic full siblings without PA defined by their ability to routinely ingest peanuts with no reactions.	Shreffler et al 2006 (103)
		Case Control	189	Japanese	Food Allergy	Diagnosis of FA was confirmed by open or blind challenge tests	Healthy controls with no history of FA	Campos et al 2007 (46)
		Case Control	226	Japanese	Food Allergy	Diagnosis of FA was confirmed by open or blind challenge tests	Non-food allergic atopic controls	Campos et al 2008 (51)
		Case Control	579	Japanese	Food Allergy and Food induced anaphylaxis	Diagnosis of FA based on either challenge tests or a definitive episode plus confirmation of antigen specific IgE levels, and FIA was defined as symptoms evoked in multiple organs	Non atopic, non asthmatic healthy controls	Hitomi et al 2009 (66)
		Case Control	204	Italian	Food Allergy (Cow's milk)	IgE-mediated provocation test to cow's milk	Non atopic, non allergic healthy controls	Galli et al 2010 (74)
		Case Control	163	European	Cow's milk allergy	Cows milk specific SPT	Atopic controls with other reported allergic symptoms	Savilahti et al 2010 (30)
		Case Control	88	European	Peanut Allergy	Clinically allergic to peanuts with an excellent history and either a peanut- specific IgE >14 IU/ml, a skin prick test >5 mm larger than negative control, or a positive double-blind, placebo-controlled food challenge.	Peanut tolerant siblings who had eaten peanuts within 3 months without a clinical reaction, and does not meet case definition criterias.	Dreskin et al 2010 (104)
		Case Control	1071	Europeans (British, Irish and Dutch)	Peanut Allergy	Oral Food Challenge	Non peanut sensitized controls with coexistent AD + The respective population controls: for English population individuals without PA, for Dutch healthy adult blood donors, and for Irish population-based Trinity Biobank control samples.	Brown et al 2011 (23)
		Case Control	117	European, Mixed, Asian, African American	Peanut Allergy	Clinically allergic to peanuts with an excellent history and either a peanut- specific IgE >14 IU/ml, a skin prick test >5 mm larger than negative control, or a positive double-blind, placebo-controlled food challenge.	Peanut tolerant siblings who had eaten peanuts within 3 months without a clinical reaction, and does not meet case definition criterias.	Dreskin et al 2011 (47)
		Case Control	89	Taiwanese	Food allergy (milk, egg white, egg yolk, shrimp, crab, soybean, codfish, mango, and peanut)	Food specific IgE level of ≥ 0.7 kU/L in response to nine food allergens.	Controls with no history of FA or systemic disease.	Chen et al 2011 (53)
		Case Control	65	Caucasian	Food Allergy	History of immediate symptoms such as skin reactions and/or respiratory tract symptoms and/or gastrointestinal symptoms and/or cardiovascular symptoms either after contact with food or ingestion of food, or both and a positive SPT to that food.	Non-allergic controls who had no history of sensitisation or allergic disease.	Gaudieri et al 2012 (54)

Supplementary Table E1: Summary of genetic studies of food allergy.

Study Type	Cohorts	Study Design	Sample (N)	Ancestry	Phenotype	Phenotype Definition		Reference
						Cases	Controls	
	Health Nuts Cohort	Case Control	920	Caucasian (1 or both parents born in Australia, Europe, the United Kingdom, North America, or New Zealand)	Food sensitization & Food Allergy	Food sensitization: SPT response of >2 mm or positive cap-FEIA results (>0.35 kU/L) to at least one of the 10 foods (egg, peanut, sesame, shrimp, cow's milk, cashew, almond, hazelnut, soy, and wheat). Food allergy: Positive OFC outcome; or a clearly objective and recent history of reaction to egg, peanut and sesame; or an SPT response of ≥8 mm to egg, peanut and sesame; or an SPT response of ≥7 mm to shrimp, cow's milk, cashew, almond, hazelnut, soy, and wheat.	Non sensitized and non allergic controls who had SPT responses of 0 mm to all foods at recruitment and in the clinic, and had negative OFC outcomes to egg/peanut.	Tan et al 2012 (24)
		Case Control	274	Brazilian	Cow's milk allergy	Anaphylaxis triggered by cow's milk or immediate clinical reactivity induced by cow's milk during a DBPCFC.	Population based healthy controls recruited from bone marrow donors.	Jacob et al 2013 (52)
		Case Control	1819	Caucasian	Peanut Allergy	Minimum requirements for inclusion- 1.) Convincing history of PA and (i) SPT ≥3 mm or (ii) Peanut specific IgE ≥0.35 kU/L 2.) No history of peanut ingestion/uncertain history of allergy and (i) SPT ≥3 mm and (ii) Peanut specific IgE ≥5 kU/L 3.) Any history suggestive of an IgE-mediated reaction not compatible with anaphylaxis and (i) SPT ≥8 mm or (ii) SPT ≥4 mm if <2 y old or (iii) Peanut specific IgE ≥15 kU/L 4.) Positive OFC	Two control groups: 1) Population based adults with self reported asthma, emphysema, and smoking history; 2) Population based new born babies (atopic status not reported).	Asai et al 2013 (25)
	Can PAR, CAPPS and SAGE Cohorts	Case Control	922	Caucasian	Peanut Allergy	(1) A convincing clinical history of allergic reaction to peanut and a positive SPT to peanut or a psIgE level ≥0.35kU/L or (2) No previous exposure to peanut or an uncertain history of an allergic reaction to peanut and either a positive SPT to peanut and a psIgE level >15 kU/L or a positive food challenge to peanut.	Non allergic, Non atopic population based controls from two other Asthma studies.	Madore et al 2013 (105)
	Isle of Wight birth cohort	Cohort study	1372	Caucasian (British)	Food Allergy & Food sensitization	(i) A reaction to a recognized food allergen such as cow's milk, hen's egg, wheat, soya, peanuts, other nuts, fish, and shellfish; (ii) A report of recognized allergic localized, skin, respiratory, abdominal symptoms or systemic reactions; and (iii) Temporal relationship	--	Venkataraman et al 2014 (26)
		Case Control	212	Turkish	Food Allergy	Titers of specific IgE ≥0.35 kU/L and a positive SPT to a food ≥3 mm; and a consistent and clear history of an early reaction related to the ingestion of the offending food; and positive open/double-blind food challenge or a clear history of anaphylaxis	Healthy children with no history of eczema, FA, allergic rhinitis, and asthma or wheezing	Buyukiryaki et al 2016 (76)
	Dutch EuroPrevall Birth Cohort	Case Control	53	Caucasian, Mixed (Caucasian and non Caucasian) & non-Caucasian	Cow's milk allergy	DBPCFC confirmed CMA	Healthy controls with no symptoms suggestive of any FA and not suffering from atopic dermatitis	Henneman et al 2016 (29)
	Health Nuts Cohort	Case Control	722	Caucasians, Asians (South-East Asians) and Mixed Asian-Caucasian	Food Allergy & Food sensitized tolerance	FA: defined by ≥1 mm SPT wheal to peanut, egg white, cow's milk or sesame and evidence of clinical reactivity by OFC. FS-tolerance: defined by ≥1 mm to peanut, egg white, cow's milk or sesame but negative OFC.	Non food allergic controls without a detectable SPT wheal to any foods at recruitment and had a subsequent negative OFC result in the clinic.	Ashley et al 2017 (36)
	Health Nuts Cohort	Case Control	722	Caucasians, Asians (South-East Asians) and Mixed Asian-Caucasian	Food Allergy, Food sensitized tolerance & Plasma IgE levels	FA: defined by ≥1 mm SPT wheal to peanut, egg white, cow's milk or sesame and evidence of clinical reactivity by OFC. FS-tolerance: defined by ≥1 mm to peanut, egg white, cow's milk or sesame but negative OFC.	Non food allergic controls without a detectable SPT wheal to any foods at recruitment and had a subsequent negative OFC result in the clinic.	Ashley et al 2017 (59)
		Case Control	2743	Japanese	Food Allergy	Positive OFC or a definitive clinical history after food intake	Healthy controls who had never been diagnosed with bronchial asthma and/or atopic dermatitis	Hirota et al 2017 (28)
		Case Control	58	Algerian	Cow's milk allergy	Positive SPT >3 mm, specific IgE >0.35 kU/L to cow's milk proteins and confirmed by an oral challenge and clinical history.	Controls without any allergies	Rahmoun et al 2017 (69)
	Geneva Cohort	Case Control	369	Caucasian	Food Allergy (Peanut & Cow's milk), Peanut or Cow's milk-specific IgE, Dose sensitivity to food allergen, and severity of the food-allergic reaction during the DBPCFC.	Food allergy defined by any positive DBPCFC.	Non allergic, Non atopic family based control.	van Ginkel et al 2018 (42)
GWAS	German Genetics of Food Allergy Study	Case Control	4224	German	Food Allergy	Diagnosis by DBPCFC	Population based cohort for cardiovascular disease / unphenotyped for food allergy	Marenholz et al 2018 (77)
	Chicago Food Allergy Study	Family based: cases and parents	2197 497 588	European Non-European Caucasian	Food allergy (9 foods), Peanut allergy, Egg allergy, Milk allergy	A convincing history of clinical reaction on ingestion of a specific food. Evidence of sensitization to the same food, defined as having a detectable food-specific IgE(>=0.10 kU L-1) and/or positive SPT with mean wheal diameter >= 3mm.	Family based controls that did not meet case definition	Hong et al 2015 (81) Liu et al 2018 (82)
	Health Nuts Study	Case Control	221	Asian, European, Mixed European Asian	Peanut allergy	Cases were defined as having a SPT >= 2mm above the negative control, or specific IgE >0.35 kU/L to peanut on the day of challenge, with evidence of clinical reactivity during oral peanut challenge.	Non-allergic by skin prick test to panel of common food allergens and safely tolerated oral peanut challenge	Martino et al 2016 (83)
	German Genetics of Food Allergy Study	Case Control	2884	European	Peanut allergy, Food allergy, Hen's egg allergy, Cow's Milk allergy	Diagnosis of food allergy was based on OFCs.	Population based cohort for cardiovascular disease / unphenotyped for food allergy	Marenholz et al 2017 (84)
	Can PAR	Case Control	1766	Caucasian	Peanut allergy	History of an allergic reaction; SPT to peanut >= 3mm and peanut specific IgE >= 0.35 kU/L. Some participants were ascertained based on their OFCs.	Non allergic, Non atopic population based controls	Asai et al 2018 (85); Asai et al 2018 (86)
	Luna Luna	Case Control	11011	Japanese	Kiwi, peach, Chinese yam, eggs, mackrel, crab, shrimp	Response to food allergy questionnaire as to whether an individual had either mild or severe allergic reactions.	Population based controls that did not meet case definition	Khor et al 2018 (87)

Supplementary Table E1: Summary of genetic studies of food allergy.

Study Type	Cohorts	Study Design	Sample (N)	Ancestry	Phenotype	Phenotype Definition		Reference
						Cases	Controls	
	Learning Early About Peanut allergy	Case Control	556	European, Afro Carribean, Mixed, Chinese, Middle Eastern or Other	Peanut allergy	Positive result on a double-blind, placebo controlled oral food challenge at 60 months of age in peanut avoidance arm.	Non-peanut allergic children who had severe eczema and/or allergy at baseline in the peanut avoidance arm.	Winters et al 2019 (31)
	Children's Hospital of Philadelphia Health Care Network	Case Control	4337	European American African American	Food allergy	History consistent with food allergy documented by an allergy specialist (timing and symptoms after ingestion); food allergy sensitivity (as shown by IgE : 0.35 kUa/l or skin prick testing >3 mm wheal); and food allergen identified as milk, egg, peanut, tree nut, soy, wheat, fish, or shellfish.	Without ICD9 code for food allergy in the medical record	Li et al 2015 (89)
G*E	The Manchester Asthma and Allergy Study	Case Control	623	Caucasian	Peanut Allergy	Peanut SPT sensitization was defined as a mean wheal diameter ≥3 mm. Peanut allergy was determined on results of open OFCs.	Either IgE to Ara h 1, 2, or 3 levels <0.35 kUa/L (8 years) or < 0.35 ISU (11 years) or passed OFC.	Brough et al 2014 (111)
	Health Nuts Study	Case Control	607	Caucasian & Asian	Food Allergy	Cases were defined as having a SPT ≥2mm above the negative control, or specific IgE >0.35 kU/L to peanut on the day of challenge, with evidence of clinical reactivity during oral peanut challenge.	Non-allergic by skin prick test to panel of common food allergens and safely tolerated oral peanut challenge	Koplin et al 2015 (112)

Supplementary Table 2: Genetic variants reported as having significant associations with food allergy identified through the candidate gene based approach. Odds ratio and P-values of the associated risk alleles are given. If a SNP is associated with more than one phenotype, phenotype abbreviation is given in the parentheses with association results. Associations marked with # have a reported replication evidence within the paper. If an association is not #, it represents either no replication or not tested for replication. Genes marked with ** are allergic diseases and FA GWAS identified loci tested for the associations with FA.

Study Design	Outcome	Cohort and Ancestry	Sample size (Case/Control)	Gene name	Associated SNPs/Alleles	Effect size (OR/β/Z)	P-value	Reference
Case control	Food allergy	Caucasian (Polish)	136/124	NAT2	NAT2*5 NAT2*6 NAT2*7	NR	NR	Gawron'ska-Szklarz et al 2001 (60)
Case control	Nut allergy	Caucasian (British)	NA=71; Atopic=45/184	STAT6	+2964 G/A	3.9	2x10 ⁻⁴	Amoli et al 2002 (40)
Case control	Food allergy	European American, African American, Other	77/61	CD14	-159 C/T	1.7	0.03	Woo et al 2003 (45)
Case control	Food allergy	Japanese	91/26	SPINK5	+1258 G/A	NR	0.03	Kusunoki et al 2005 (35)
Case control	Food allergy	Japanese	111/115	IL10	-1082 A/G	2.4	0.04	Campos et al 2008 (51)
Case control	Food induced anaphylaxis	Japanese	325/254	NLRP3	-2189 G/A 1979 G/A 4240 T/C 16974 C/T 22162 A/C 29940 C/G 31792 C/T	1.81 1.77 1.71 1.81 1.53 1.8 1.71	0.021 9.1x10 ⁻⁴ 0.0029 8.6x10 ⁻⁴ 0.013 6.8x10 ⁻⁴ 0.0021	Hitomi et al 2009 (66)
Case control	Peanut Allergy	European (British, Irish & Dutch)	71/1000	FLG	Null Genotype (R501X and 2282del4)#	5.3	3.0x10 ⁻⁶	Brown et al 2011 (23)
Case control	Peanut Allergy	European, Mixed, Asian, African American	53/64	CD14	rs2569190	1.97	0.03	Dreskin et al 2011 (47)
Case control	Food allergy	Caucasian	30/35	IL28B	rs12979860	3	0.04	Gaudieri et al 2012 (54)
Case control	Food Sensitization	Caucasian	794/126	FLG	Null mutations (R501X, 2282del4, R2447X, S3247X, and 3702delG)	3	0.043	Tan et al 2012 (24)
Case control	Cow's milk allergy	Brazilian	50/224	IL10	-1082 G/A	1.74	0.01	Jacob et al 2013 (52)
Case control	Peanut Allergy	Caucasian	663/1156	FLG	Null mutations (R501X, 2282del4, R2447X and S3247X)	1.96	5.12x10 ⁻⁷	Asai et al 2013 (25)
Longitudinal cohort study	Food allergy	Caucasian (British)	1373 (10 y), 1313 (18 y)	FLG	Null mutations (R501X, 2282del4, S3247X, 3702delG, and R2447X)	2.9 (10 y) 2.5 (18 y)	0.022 0.032	Venkataraman et al 2014 (26)
Case control	Cow's milk allergy	Caucasian (Dutch), Mixed (Caucasian and non-Caucasian) & non-Caucasian	30/23	TLR10/1/6 FAM114A1 ** IL2 IL21 KIAA1109**	rs17616434 rs2069772	NR NR	0.002 0.03	Henneman et al 2016 (29)
Case control	Food allergy & Food sensitized tolerance	Caucasians, Asians (South-East Asians) and Mixed Asian-Caucasian	FA=367, FST=199 /156	SPINK5	rs9325072# rs3815741# rs4705054# rs9325071#	2.95 (FA) 2.11 (FST) 2.76 1.94 1.83	0.001 0.04 0.002 0.01 0.02	Ashley et al 2017 (36)
Case control	Food Allergy, Food sensitized tolerance & Plasma IgE levels	Caucasians, Asians (South-East Asians) and Mixed Asian-Caucasian	FA=367, FST=199 /156	IL13	rs1295686# rs3091307# rs1800925# rs1295683#	1.75 (FA) 0.38 (IgE) 0.29 (IgE) 0.26 (IgE) 0.29 (IgE)	0.003 3.0x10 ⁻⁴ 0.007 0.02 0.03	Ashley et al 2017 (59)
Case control	Food allergy	Japanese	872/1871	C11ORF30 LRRC32** TMEM232 SLC25A46 ** TNFRSF6B ZGPAT ** OVOL1 ** KIF3A IL13 ** GLB1 ** CCDC80 ** ZNF365 ** OR10A3 NLRP10 ** IL2 IL21 ** CLEC16A DEXI ** ZNF652 ** TSLP WDR36 ** STAT6 ** FLG	rs11236809 rs9326801 rs6010620 rs593982 rs1295686 rs6780220 rs12634229 rs10995251 rs878860 rs17389644 rs2041733 rs16948048 rs3806932 rs167769 Null mutations (c.3321delA, p.Q1701*, p.S2554*, p.S2889*, p.S3296*, and p.K4022)	1.34 1.19 1.14 1.15 1.4 1.32 1.25 1.25 1.16 1.27 1.16 1.27 1.18 1.25 1.63	1.4x10 ⁻⁵ 0.031 0.039 0.016 6.7x10 ⁻⁸ 2.5x10 ⁻⁶ 2.8x10 ⁻⁴ 1.3x10 ⁻⁴ 0.01 0.0096 0.019 0.0039 0.012 0.0014 5.5x10 ⁻⁵	Hirota et al 2017 (28)
Case control	Cow's milk allergy	Algerian	30/28	cREL	+7883 G/T	4.11	4.0x10 ⁻⁴	Rahmoun et al 2017 (69)
Food Allergy						2.10 (FA) 2.37 (PA)	0.036 0.018	

Supplementary Table 2: Genetic variants reported as having significant associations with food allergy identified through the candidate gene based approach. Odds ratio and P-values of the associated risk alleles are given. If a SNP is associated with more than one phenotype, phenotype abbreviation is given in the parentheses with association results. Associations marked with # have a reported replication evidence within the paper. If an association is not #, it represents either no replication or not tested for replication. Genes marked with ** are allergic diseases and FA GWAS identified loci tested for the associations with FA.

Study Design	Outcome	Cohort and Ancestry	Sample size (Case/Control)	Gene name	Associated SNPs/Alleles	Effect size (OR/β/Z)	P-value	Reference
Case control	(Peanut & Cow's milk), Peanut or Cow's milk specific IgE, severity of the food allergic reaction during the DBPCFC, and Eliciting dose	Caucasian	262/107	STAT6	rs324015	2.06 (psIgE)	0.039	van Ginkel et al 2018 (42)
						2.13 (PAsev)	0.033	
						2.56 (PA ED)	0.011	
						2.81 (cmsIgE)	0.005	
						2.49 (FA)	0.013	
					rs1059513	2.41 (PA)	0.016	
						2.20 (psIgE)	0.028	
						2.27 (PAsev)	0.024	
						2.17 (PA ED)	0.03	
						2.43 (CMsev)	0.015	
Case control	Food allergy	German	866/3358	C11ORF30 LRRC32**	rs7936434	2.26 (CM ED)	0.024	Marenholz et al 2018 (77)
						1.34 (FA)	1.6x10 ⁻⁷	
						1.28 (PA)	0.0024	

Supplementary Table E3 : Summary of all GWAS for food allergy. Ancestry and number of participants for the specific phenotype in the discovery cohort are given. Genome-wide and suggestive significance threshold for each study, and SNPs showing association at the specified threshold are presented. Allele frequency, effect estimates and p-value of the risk allele are shown. Loci marked with * have a reported replication evidence within the paper. If an association is not *, it represents either no replication or not tested for replication. Loci marked with ** have a replication evidence from multiple papers.

Study Design	Cohort and Ancestry	Sample size (Case/Control)	Significance threshold (G/S)	Outcome	Locus name	Peak SNPs/CNVs	AF	Effect size (OR/RR)	P-value	Reference
GWAS	USA (European)	2197 (316/1881)	P < 5x10-8 P < 1x10-7	Peanut allergy	HLA-DQB1 HLA-DQA2 *,** HLA-DRA*,**	rs9275596 rs7192	0.35 0.39	1.7 1.7	6.8x10-10 5.5x10-8	Hong et al 2015 (81)
Maternal genetic effect GWAS	USA (European)	588 FA:(482/19/59/28) PA:(247/7/33/14) EA:(169/5/19/8)	P < 5x10-8 P < 5x10-7	Food allergy	LOC101927947 GYG1P2 RNU6-67P	rs4235235 rs976078	0.06 0.09	0.36 2.14	4.82x10-8 3.78x10-7	Liu et al 2018 (82)
Parent of origin effect GWAS				Egg allergy	ZNF652 ZNF652	rs1343795 rs4572450	0.21 0.37	0.37 0.37	4.47x10-7 4.47x10-7	
				Peanut allergy	ADGB	rs4896888	0.44	0.15	2.66x10-7	
GWAS	Australia (Asian, European, Mixed European/Asian)	221 (73/148)	P < 5x10-8 P ≤ 5x10-5	Peanut allergy	SLC2A9	rs10018666	0.76	5.86	4x10-8	Martino et al 2016 (83)
					PLAGL1	rs6928827	0.88	13.98	1x10-7	
					LMX1A	rs6686894	0.11	0.06	4x10-7	
					BCAS1	rs11700330	0.22	0.23	3x10-6	
					RGS21	rs12142904	0.24	3.51	5x10-6	
					IER5L	rs4240433	0.77	3.61	7x10-6	
					IL26	rs7300806	0.8	0.28	1x10-5	
					MDN1	rs9362681	0.31	2.83	1x10-5	
					FXR1	rs6763069	0.63	0.38	2x10-5	
					NAV2	rs2439871	0.59	0.38	1x10-5	
					SALL3	rs73971133	0.06	0.07	3x10-5	
					TES	rs73220497	0.08	0.06	3x10-5	
					ATP10A	rs17555239	0.43	2.58	3x10-5	
					RIMS2	rs16870788	0.16	3.58	3x10-5	
					PAFAH1B1	rs8077351	0.07	0.05	3x10-5	
					SORBS2	rs57144668	0.65	0.37	3x10-5	
					PAX2	rs6584390	0.76	3.56	4x10-5	
					LINGO2	rs10812871	0.53	0.38	4x10-5	
GWAS	German (European)	2884 FA:(497/2387) PA:(220/2387) EA:(288/2387)	P < 5x10-8 P value for entering in replication: P < 1x10-3	Food allergy	IL4 KIF3A* FLG-AS1* C11orf30 LRRC32 *,** SERPINB7*	rs11949166 rs12123821 rs2212434 rs12964116	0.72 0.06 0.71 0.46	0.6 2.55 1.29 1.9	1.2x10-13 8.4x10-10 3.4x10-4 5.7x10-6	Marenholz et al 2017 (84)
				Peanut allergy	HLA-DQB1*,**	rs9273440	0.05	0.66	6.6x10-7	
				Egg allergy	SERPINB7/B2*	rs1243064	0.26	1.65	1.6x10-7	
					DLX2 ITGA6*	rs115218289	0.02	0.18	1.80x10-8	
					ARHGAP24*	rs744597	0.4	0.61	3.98x10-7	
					CHCHD3 EXOC4*	rs78048444	0.02	0.22	5.44x10-7	
						rs7475217	0.38	1.64	3.58x10-7	
						rs71193762	0.38	1.63	3.77x10-7	
						rs2394283	0.38	1.64	4.42x10-7	
						rs12779828	0.38	1.63	4.66x10-7	
						rs2394298	0.38	1.62	5.73x10-7	
						rs34018067	0.38	1.62	5.73x10-7	
						rs7911791	0.38	1.62	6.04x10-7	
						rs11815638	0.38	1.62	6.04x10-7	

Supplementary Table E3 : Summary of all GWAS for food allergy. Ancestry and number of participants for the specific phenotype in the discovery cohort are given. Genome-wide and suggestive significance threshold for each study, and SNPs showing association at the specified threshold are presented. Allele frequency, effect estimates and p-value of the risk allele are shown. Loci marked with * have a reported replication evidence within the paper. If an association is not *, it represents either no replication or not tested for replication. Loci marked with ** have a replication evidence from multiple papers.

Study Design	Cohort and Ancestry	Sample size (Case/Control)	Significance threshold (G/S)	Outcome	Locus name	Peak SNPs/CNVs	AF	Effect size (OR/RR)	P-value	Reference
GWAS	Canadian (Caucasian)	1766 (850/926)	P≤3.6x10-8 P≤1.49x10-6	Peanut allergy	C11orf30 LOC101928813*,**	rs11816216	0.38	1.62	6.04x10-7	Asai et al, 2017 (85)
						rs61866029	0.38	1.62	6.04x10-7	
						rs7910177	0.38	1.62	6.04x10-7	
						rs7894410	0.38	1.62	7.42x10-7	
						rs748704	0.37	1.6	1.06x10-6	
						rs7936070	0.49	1.57	7.81x10-7	
						rs7936312	0.49	1.57	7.81x10-7	
						rs7936323	0.49	1.57	7.81x10-7	
						rs7931483	0.49	1.58	5.44x10-7	
						rs7936434	0.49	1.58	5.17x10-7	
					MMP12 MMP13*	rs144897250	0.02	6.2	2.90x10-7	
						rs16957085	0.09	2.06	1.23x10-6	
					LOC101927166*	rs56311919	0.09	2.06	1.23x10-6	
						rs55765969	0.09	2.06	1.23x10-6	
						rs139462954	0.09	2.06	1.23x10-6	
						rs72827854	0.09	2.16	2.60x10-7	
					SKAP1*	rs56151068	0.1	2.06	9.58x10-7	
						rs200314279	0.1	2.06	6.36x10-7	
						rs4491576	0.1	2.09	6.70x10-7	
						rs17623518	0.1	2.06	9.58x10-7	
						rs17695179	0.1	2.06	9.58x10-7	
						rs111396120	0.1	2.06	9.58x10-7	
						rs143328356	0.1	2.06	9.58x10-7	
						rs17623125	0.1	2.06	9.58x10-7	
						rs17623416	0.1	2.06	9.58x10-7	
						rs2175156	0.1	2.06	9.58x10-7	
						rs72827825	0.1	2.06	9.58x10-7	
						rs72827848	0.1	2.06	9.58x10-7	
						rs16956001	0.1	2.06	9.58x10-7	
						rs72827851	0.1	2.06	9.58x10-7	
						rs16955960	0.1	2.06	1.01x10-6	
						rs56093336	0.09	2.06	1.01x10-6	
						rs143892933	0.09	2.06	1.06x10-6	
						rs16956501	0.09	2.06	1.12x10-6	
						rs55912545	0.09	2.06	1.12x10-6	
						rs55641965	0.09	2.06	1.12x10-6	
						rs72827805	0.1	2.04	1.23x10-6	
						rs112147946	0.1	2.05	1.23x10-6	
						rs72827806	0.1	2.05	1.23x10-6	
						rs17694670	0.1	2.05	1.23x10-6	
						rs72827810	0.1	2.05	1.23x10-6	
						rs17621689	0.1	2.05	1.23x10-6	
						rs138636532	0.09	2.06	1.23x10-6	
						rs17694404	0.1	2.04	1.30x10-6	
						rs147813436	0.1	2.04	1.30x10-6	
						rs17694168	0.1	2.04	1.30x10-6	
						rs17694092	0.1	2.04	1.30x10-6	
						rs72825596	0.1	2.04	1.30x10-6	
						rs10514944	0.09	2.05	1.37x10-6	
					ANGPT4*	rs523865	0.23	0.57	4.42x10-7	
						rs1049213	NR	NR	1.82x10-11	

Supplementary Table E3 : Summary of all GWAS for food allergy. Ancestry and number of participants for the specific phenotype in the discovery cohort are given. Genome-wide and suggestive significance threshold for each study, and SNPs showing association at the specified threshold are presented. Allele frequency, effect estimates and p-value of the risk allele are shown. Loci marked with * have a reported replication evidence within the paper. If an association is not *, it represents either no replication or not tested for replication. Loci marked with ** have a replication evidence from multiple papers.

Study Design	Cohort and Ancestry	Sample size (Case/Control)	Significance threshold (G/S)	Outcome	Locus name	Peak SNPs/CNVs	AF	Effect size (OR/RR)	P-value	Reference
GWAS	Canadian (Caucasian)	1766 (850/926)	P≤3.6x10-8 P≤1.49x10-6	Peanut allergy	HLA-DQB1*,**	rs3134976	NR	2.11	2.15x10-10	Asai et al 2018 (86)
						rs3134994	NR	2.11	2.15x10-10	
						rs3135006	NR	2.1	2.45x10-10	
						rs3134995	NR	2.1	3.17x10-10	
						rs3135190	NR	2.08	4.66x10-10	
						rs1049053	NR	2.08	4.66x10-10	
						rs1049225	NR	2.08	4.66x10-10	
						rs17612852	NR	1.99	1.86x10-9	
						rs9275596	NR	1.76	1.04x10-7	
						rs1612904	NR	1.76	1.36x10-7	
						rs3135002	NR	1.97	1.61x10-7	
						rs7774434	NR	0.58	2.22x10-7	
						rs1049056	NR	0.47	2.75x10-7	
						rs4947344	NR	1.71	4.19x10-7	
						rs1794275	NR	0.51	8.22x10-7	
						rs7767167	NR	1.95	1.12x10-7	
GWAS	Japanese (East Asian)	11011 Peach:(320/8350) Shrimp:(539/8350)	P < 4.4x10-9 P < 1.2x10-7	Shrimp allergy	HLA-DQA1, HLA-DRB5, HLA-DRB1, HLA-DQB1**, HLA-DQA2**, HLA-DRA**	rs74995702	NR	1.91	6.3x10-17	Khor et al 2018 (87)
				Peach allergy	HLA-DQA1, HLA-DRB5, HLA-DRB1	rs28359884	NR	1.8	2.3x10-12	
GWAS	British (European, Afro-Caribbean or African, Asians)	275 (48/227)	P < 5x10-8 P < 1x10-5	Peanut allergy	MALT1 ZNF532	rs57265082	0.06	10.99	6.49x10-8	Winters et al 2019 (31)
					PADI6	rs80151145	0.08	6.16	2.91x10-6	
					RCC2 ARHGEF10L	rs145726195	0.04	9.63	7.22x10-6	
					LINC00298 LINC00299	rs72777284	0.03	10.81	8.55x10-6	
					TRIM2	rs12643843	0.34	3.87	9.82x10-6	
					GNPDA1 NDFIP1	rs74326323	0.07	6.04	5.40x10-6	
					PLPP7 PRRC2B	rs11243375	0.04	12.02	2.21x10-6	
					LINC00540 BASP1P1	rs73156540	0.1	5.07	3.56x10-6	
					LINC00540 BASP1P1	rs73156541	0.1	4.97	4.26x10-6	
					LINC01568 LOC101928035	rs2526073	0.31	3.73	9.79x10-6	
					LINC01260 KCNK15-AS1	rs6031719	0.43	3.82	6.60x10-6	
					UGCGL2	chr13:96537274-9	NR	NR	2.84x10-5	
GWAS (CNV)	USA (European American, African American)	4337 (357/3980)	P < 5x10-4	Food allergy	CPSF3L, GLTPD1, PUSL1	chr1:1176597-245	NR	NR	3.27x10-4	Li et al 2015 (89)
					GALNTL6	chr4:172367540-1	NR	NR	3.62x10-4	

Table E4: Associations of HLA alleles, haplotypes and amino acids with food allergies. If a variant is associated with more than one phenotype, phenotype abbreviation is given in the parentheses with association results. NR = no reported OR/RR.

Cohort and Ancestry	Sample size (Case/Control)	Significance threshold	Outcome	Alleles/Amino Acids/Haplotypes	Effect size (OR/RR)	P-value	Reference
Caucasian (German)	Pollen associated FA=80; Con=4251	p<0.0038	Peanut Allergy Carrot Allergy	HLA-DRB1*08 HLA-DRB1*12	6.04 13.01	0.0013 <1x10 ⁻⁶	Boehncke et al 1998 (101)
Caucasian (British)	PA=50; Rel Con=111; Unrel Con=293	p <0.05 (corrected for # alleles for each locus)	Peanut Allergy	HLA-DRB1*08 HLA-DQB1*04	4.37 6.79	0.0021 (0.027) 0.00042 (0.0029)	Howell et al 1998 (102)
Caucasian and Mixed	NA=84; Atopic=82; Controls=1798	p <0.05 (corrected for # of comparisons)	Nut allergy	HLA-B*07 HLA-DRB1*11 HLA-DRB1*13 HLA-DQB1*06	NR NR NR NR	<0.02 (0.53) <0.02 (0.70) <0.05 (0.82) <0.01 (0.37)	Hand et al 2004 (106)
Caucasian & Asian	73/75	p<0.05(corrected for # alleles tested)	Peanut Allergy	*0301, *0304, *0305, *0309, *0310, *0312, *0313	NR	0.04 (0.3)	Shreffler et al 2006 (103)
European	44/44	p<0.05(corrected for # alleles tested)	Peanut Allergy	HLA-DRB1*0803	NR	7.7x10 ⁻¹¹ (4.5x10 ⁻⁹)	Dreskin et al 2010 (104)
Caucasian (Finnish)	87/76	ps0.003	Cow's milk Allergy IgE mediated Cow's milk Allergy	Carriers ((DR1/10)-DQB1*0501 & (DR15)-DQB1*0602)	NR NR NR NR NR NR NR NR	0.0001 (BLG IgG) 0.003 (CAS IgG) <0.0001 (BLG IgG4) <0.0001 (CAS IgG4) <0.0001 (BLG IgG) 0.001 (CAS IgG) 0.002 (BLG IgG4) 0.001 (CAS IgG4)	Savilahti et al 2010 (30)
Caucasian	590/332	P<0.05(corrected for # alleles tested)	Peanut Allergy	HLA-DQB1*02 HLA-DQB1*03:02 HLA-DQB1*05 HLA-DQB1*05:01 HLA-DQB1*06:03	0.12 0.52 0.21 0.25 2.59	1.1x10 ⁻¹⁶ (1.3x10 ⁻¹⁵) 2.2x10 ⁻³ (2.6x10 ⁻²) 2.5x10 ⁻⁴ (3.0x10 ⁻³) 7.7x10 ⁻⁶ (9.3x10 ⁻⁵) 1.6x10 ⁻⁴ (1.9x10 ⁻³)	Madore et al 2013 (105)
European	2197 (316/1881)	p < 5x10 ⁻⁸	Peanut Allergy	HLA-DQA1*01:02 HLA-DQB1*06 AA_DRB1_71 AA_DQA1_207 AA_DQB1_-5 AA_DQB1_26 AA_DQB1_86 AA_DQB1_125 AA_DQB1_130	NR NR NR NR NR NR NR NR NR	4.5x10 ⁻⁸ 5.4x10 ⁻⁹ 2.3x10 ⁻¹⁰ 2.7x10 ⁻⁸ 3.7x10 ⁻⁸ 1.1x10 ⁻⁸ 1.6x10 ⁻⁸ 5.4x10 ⁻⁹ 1.6x10 ⁻⁸	Hong et al 2015 (81)
Asian, European, Mixed European/Asian	221 (73/148)	p < 5x10 ⁻⁸	Peanut Allergy	AA_DRB1_37 AA_DRB1_71 AA_DRB1_37 AA_DRB1_47 HLA-DQB1*06 HLA-DPB1*03 HLA-DQA1*02 HLA-DRB1*15 HLA-DRB1*07 HLA-DPB1*03:01 HLA-DQA1*02:01 HLA-DRB1*07:01 HLA-DQB1*06:02 HLA-DQA1*01:02	0.3 0.34 0.34 0.35 2.26 3.23 0.36 2.15 0.34 3.23 0.36 0.34 2.11 1.81	9.8x10 ⁻⁵ 1.5x10 ⁻⁴ 2.16x10 ⁻⁴ 2.76x10 ⁻⁴ 1.20x10 ⁻³ 4.25x10 ⁻³ 1.48x10 ⁻² 1.60x10 ⁻² 1.68x10 ⁻² 4.25x10 ⁻³ 1.48x10 ⁻² 1.68x10 ⁻² 1.72x10 ⁻² 1.75x10 ⁻²	Martino et al 2016 (83)
	Peach (320/8350)		Peach Allergy	HLA-DRB1*09:01 HLA-DRB1*14:05 HLA-DRB1*15:01 HLA-DRB1*15:02 HLA-DQB1*03:03 HLA-DQB1*06:02 HLA-DQB1*05:03 HLA-DQB1*06:01 HLA-DPB1*14:01 HLA-DPB1*09:01 HLA-DRB1*09:01-HLA-DQB1*03:03 HLA-DRB1*14:05-HLA-DQB1*05:03 HLA-DRB1*15:01-HLA-DQB1*06:02 HLA-DRB1*15:02-HLA-DQB1*06:01 HLA-DRB1*14:05-HLA-DQB1*05:03-HLA-DPB1*05:01 HLA-DRB1*15:01-HLA-DQB1*06:02-HLA-DPB1*02:01 HLA-DRB1*09:01-HLA-DQB1*03:03-HLA-DPB1*05:01 HLA-DRB1*15:02-HLA-DQB1*06:01-HLA-DPB1*09:01 HLA-DRB1*09:01-HLA-DQB1*03:03-HLA-DPB1*02:01 HLA-DRB1*04:05 HLA-DRB1*15:01 HLA-DQB1*04:01 HLA-DQB1*06:02 HLA-DPB1*06:01 HLA-DPB1*14:01 HLA-DRB1*04:05-HLA-DQB1*04:01 HLA-DRB1*15:01-HLA-DQB1*06:02 HLA-DRB1*04:05-HLA-DQB1*04:01-HLA-DPB1*05:01 HLA-DRB1*04:05-HLA-DQB1*04:01-HLA-DPB1*02:01 HLA-DRB1*04:05-HLA-DQB1*04:01-HLA-DPB1*04:02	1.67 2.45 1.75 1.67 1.65 1.7 1.99 1.61 2.38 1.37 1.68 2.46 1.80 1.68 2.23 1.77 1.52 1.54 1.77 2.00 1.56 1.96 1.59 5.24 1.98 1.90 1.55 1.83 2.11 1.66	1.79x10 ⁻⁷ 9.98x10 ⁻⁶ 2.69x10 ⁻⁵ 4.82x10 ⁻⁵ 1.41x10 ⁻⁷ 8.23x10 ⁻⁵ 3.40x10 ⁻⁵ 1.28x10 ⁻⁵ 2.27x10 ⁻³ 1.00x10 ⁻² 1.15x10 ⁻⁷ 9.38x10 ⁻⁶ 1.48x10 ⁻⁵ 4.31x10 ⁻⁵ 9.70x10 ⁻⁴ 8.79x10 ⁻⁴ 1.98x10 ⁻³ 1.10x10 ⁻³ 2.82x10 ⁻⁴ 2.22x10 ⁻¹⁶ 4.56x10 ⁻⁵ 2.22x10 ⁻¹⁶ 2.24x10 ⁻⁵ 8.86x10 ⁻⁵ 5.63x10 ⁻³ 3.92x10 ⁻¹⁹ 8.07x10 ⁻⁵ 2.33x10 ⁻¹⁰ 5.70x10 ⁻⁵ 9.80x10 ⁻³	Khor et al 2018 (87)
Japanese (East Asian)	Shrimp (539/8350)	P < 0.05	Shrimp Allergy				

Current Insights Into The Genetics Of Food Allergy.

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Online Repository Figure Legend

Fig S1: Fold enrichment of FA genes in gene sets with significant pathway enrichment. The full list of genes from Table 1 were input into Panther for gene set enrichment analysis. We limit the results presented in the figure to those genes sets with <500 genes, and with an FDR<E-04, and show an abundance of gene sets pertaining to adaptive and innate immunity.

SUPP FIG 1

Fold Enrichment in gene sets with FDR<E-04

