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Genetic determinants of paediatric food allergy: A systematic review

Short title: Genetic basis of food allergy: A systematic review

Noor H. A. Suaini[1,2], Yichao Wang[1,2], Victoria X. Soriano[1,2], David J. Martino[1,2,3], Katrina J. Allen[1,2,4,5], Justine A. Ellis[1,6,7], Jennifer J. Koplin[2,8]

Affiliations:

[1]Department of Paediatrics, University of Melbourne, Parkville, Victoria, Australia

[2]Centre for Food and Allergy Research, Murdoch Children's Research Institute, Parkville, Victoria, Australia

[3]Telethon Kids Institute, University of Western Australia, Perth, Australia.

[4]Department of Allergy and Clinical Immunology, Royal Children's Hospital, Parkville, Victoria, Australia

[5]Institute of Inflammation and Repair, University of Manchester, Manchester, United Kingdom.

[6]Genes, Environment & Complex Disease, Murdoch Children's Research Institute, Parkville, Victoria, Australia

[7]Centre for Social and Early Emotional Development, Faculty of Health, Deakin University, Burwood, Victoria, Australia.

[8]School of Population and Global Health, University of Melbourne, Parkville, Victoria, Australia

Corresponding Author:

Dr Jennifer J. Koplin

Murdoch Children's Research Institute

Royal Children's Hospital, Flemington Road,

Parkville 3052, Victoria, Australia

Email: jennifer.koplin@mcri.edu.au

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Abbreviations:

CNV: Copy Number Variations

CNVR: Copy Number Variations Region

GWAS: Genome Wide Association Study

SNP: Single Nucleotide Polymorphisms

UTR: Untranslated Region

ABSTRACT

Background

The genetic determinants of food allergy have not been systematically reviewed. We therefore systematically reviewed the literature on the genetic basis of food allergy, identifying areas for further investigation.

Methods

We searched three electronic databases (Medline, Embase and PubMed) through to 9th January 2018. Two authors screened retrieved articles for review according to inclusion criteria and extracted relevant information on study characteristics and measures of association. Eligible studies included those that reported an unaffected non-atopic control group, had genetic information, and were carried out in children.

Results

Of the 2088 studies retrieved, 32 met our inclusion criteria. Five were genome-wide association studies and the remaining were candidate gene studies. 22 of the studies were carried out in a predominantly Caucasian population with the remaining 10 from Asian-specific populations or unspecified ethnicity. We found *FLG, HLA, IL10, IL13,* as well as

some evidence for other variants (*SPINK5, SERPINB, C11orf30*) that are associated with food allergy.

Conclusions

Little genetic research has been carried out in food allergy, with *FLG, HLA* and *IL13* being the most reproducible genes for an association with food allergy. Despite promising results, existing genetic studies on food allergy are inundated with issues such as inadequate sample size and absence of multiple testing correction. Few included replication analyses or population stratification measures. Studies addressing these limitations along with functional studies are therefore needed to unravel the mechanisms of action of the identified genes.

INTRODUCTION

Food allergy is a complex multifactorial disease with both environmental and genetic risk factors thought to contribute to its pathogenesis. It elicits abnormal immunological reaction upon exposure to certain food proteins, resulting in adverse clinical reactions, most severely anaphylaxis, which can be life-threatening (1).

Existing twin and family studies have shown that genetic composition may play a significant role in the development of food allergy (2-4). In these studies, genetic differences contribute about 15% to 35% of the observed individual differences in food-specific IgE (4). Twin studies found that monozygotic twins recorded higher concordance rates for sensitisation to peanut allergen than dizygotic twins (2, 3). Sicherer et al found that the heritability estimate for peanut allergy was 82% to 87% (3), demonstrating the role of genetic influence as those with more similar genes (monozygotic twins) were likely to have a more similar phenotype.

The prevalence of food allergy in infants and children below 5 years old appears to be higher in Western countries, compared with Asian countries (5) . However, Australian-born children of Asian parents have a higher prevalence of food allergy compared with both Asian children born in Asia and Australian-born Caucasian children (6, 7). This suggests that the effect of genetic predisposition on food allergy may differ depending on environmental exposures in early life.

Both candidate gene and genome-wide association studies (GWAS) have attempted to identify genes associated with food allergy. An increasing number of GWAS are being carried out primarily for 'any food allergy' and peanut allergy outcomes, identifying novel genes associated with these allergies. However, these studies were predominantly in Caucasian or European populations. Candidate gene studies have targeted immune-related genes postulated to be involved in the mechanisms of food allergy. Additionally, given that there are shared genetic risk factors among asthma, allergic rhinitis and eczema (8, 9), there has been work to examine genes previously associated with other allergic diseases for an association with food allergy. However, compared to other allergic diseases, the genetic basis of food allergy remains relatively under-explored. The main objective of this systematic review is to examine the evidence for the association between genetic polymorphisms and food allergy and identify areas that need further investigation.

METHODS

This systematic review was conducted according to a previously developed protocol registered on the international prospective register of systematic reviews (PROSPERO) and reported according to the PRISMA checklist (10).

Search methods for identification of studies

Electronic searching

We searched three databases: Medline (Ovid), Embase (Ovid) and PubMed for references using MeSH terms and thesaurus/keywords on 9th January 2018. PubMed was searched only using keywords to retrieve electronic publications and papers not yet indexed in Medline or Embase. Results were limited to English language and studies of children 0-18 years old. The search strategy was formulated with the help of an experienced librarian at the Royal Children's Hospital and was first developed in Medline (Ovid) and adapted in other databases. The complete search terms and strategies used are listed in the Online Repository Tables S1-S2.

We additionally hand-searched reference lists of reviews and meta-analyses to include any citations that contained information on genetic association of food allergy not captured by the above strategy.

Inclusion criteria of studies

Type of studies

We included cross-sectional studies, case-control studies, prospective, retrospective longitudinal studies (cohorts, case-control studies), family linkage studies, sibling-pair studies, and randomised control trials in our search strategy.

However, only studies that fulfilled the following criteria were included in our final review:

- Presence of unaffected non-atopic control groups in study design
- Study was carried out in children. Studies that spanned childhood and adulthood were also included.
- Studies examined association between food allergy and single nucleotide polymorphisms (SNPs), haplotypes or copy number variants (CNVs).

Case reports and case series were excluded. These often described rare mutations among individual patients with food allergy. Systematic reviews, meta-analyses, conference abstracts, non-original articles (comments, editorials, book chapters) and animal studies were also excluded. Studies carried out in patients with other pre-existing diseases (such as those with food protein-induced enterocolitis syndrome, autism, eosinophilic esophagitis or any other conditions) apart from food allergy were also excluded.

Type of outcomes

The main outcome of the systematic review is clinical food allergy. Studies were included if food allergy diagnosis was determined by an i) oral food challenge or ii) a combination of positive skin prick test and/or specific IgE levels and information on history of food allergy.

Quality assessment

Study quality was assessed by a points scoring system comprising of study reproducibility, study design and statistical analyses, adapted from previous studies (11, 12). These studies based their quality assessments on published checklist and recommendations on replicating genotype-phenotype associations (13) and design of genetic studies in complex diseases (14). Risk of bias was assessed as a measure of study quality but was not used as a basis for inclusion or exclusion of studies. Full details on the criteria for quality assessment and scoring system are included in the Online Repository Table S3.

Data collection and synthesis

Two reviewers (NS and YW) independently screened the title and abstracts of all retrieved citations against the pre-determined inclusion and exclusion criteria. Where there was a discrepancy in labelling of included studies, the full text was reviewed by the same reviewers. Eligible papers were scrutinized to extract relevant data and assessed for study quality by two reviewers (NS and VS).

Data were extracted from each paper and compiled for each gene. We reported odds ratios with 95% confidence intervals and where available, p-values for association with food allergy as reported by the original paper.

We chose to report our findings in a narrative manner as there was insufficient data to carry out a pooled meta-analyses. In studies where several outcomes (e.g asthma, eczema) were studied apart from food allergy or its subtypes, only the results relevant to food allergy and/or its subtypes were included in the final summary of reported associations. In studies where both atopic controls and non-atopic controls were used, only data pertaining to unaffected non-atopic controls were shown.

RESULTS

Characteristics of included studies

A total of 32 articles out of 2088 reviewed met our eligibility criteria (Figure 1). The characteristics of included studies are summarized in Online Repository Table S4.

Two of these studies were gene-environment interaction studies and these studies reported that the genetic associations were only relevant in the presence of mentioned particular environmental component (15, 16).

We also identified five GWAS with either food or peanut allergy as an outcome. Four of these were carried out in children (17-20) and the other was carried out in a population across the ages of 1 to 93 years (21).

The remaining 25 articles were candidate gene studies, with 14 studies examining food allergy generally, whereas three looked at cow's milk allergy and eight at peanut allergy specifically. Of the 25 candidate gene studies, three of these studies were carried out in a population across ages ranging from 1 to 61 years old, while the remaining 22 studies were in children and young adults under 21 years of age.

Included studies were of varying sample sizes with the smallest study having 30 food allergy Caucasian cases and 35 non-allergic Caucasian controls (22) while the largest study was a GWAS with 2197 European subjects (671 with food allergy, 144 non-allergic non-sensitized controls, and 1,382 European controls of uncertain phenotype) (17). The majority (n=11) of included studies were conducted in only 'Caucasian', 'European' or 'White' populations (19, 21-30), whereas 11 studies were carried out in predominantly Caucasian populations alongside other ethnicities ('Asians', 'Mixed', 'African American') (15-18, 20, 31-36). Four others were carried out in Japanese populations (37-40), one in a Taiwanese population (41), and there were five studies where ethnicity was not mentioned (42-46).

Quality Assessment

A detailed assessment of study quality can be found in the Online Repository Table S3. 17 of the included studies were of low quality, 10 of moderate quality and the remaining five scored highly. Only half of the studies provided information on Hardy-Weinberg equilibrium (HWE) assessment (Figure 2). In terms of study design, few studies (n=6) included a measure of statistical power as part of their study. 78% of the studies included assessment of population stratification, including those that were not scored on this criteria as they restricted their analyses to one population group (Figure 2). Several studies carried out meta-analyses with additional cohorts instead of having a replication cohort, but the results were not included in this review. Only 25% of the studies carried out an independent replication cohort to validate their findings.

Genes investigated in included studies

We identified seven gene regions investigated in more than one study and presented the congruency of their findings here. A summary of these gene regions and the evidence of association with food allergy is shown in Figure 3. A detailed compilation of genes and SNPs from all eligible studies is provided in Table 1.

HLA

Human leukocyte antigen (HLA) complex has been one of the most commonly studied gene regions in current food allergy research. This gene has been investigated by nine studies, although with inconsistent findings. Studies investigating *HLA* were widely heterogeneous primarily due to the highly polymorphic nature of the HLA region and the different variant classes. Some studies analysed the classical two or four digit alleles while others analysed the specific HLA protein, amino acid polymorphisms or SNPs within the gene. A study by Li et

al however was the only study that investigated candidate genes as well as CNV and CNV regions (CNVR) in a genome-wide dataset (18). In its candidate gene analysis, rare CNVs of duplication in the gene HLA-B at chr6:31300691-31304663 was detected in two food allergy cases and three control samples.

Associations with SNPs

In the first GWAS of food allergy by Hong et al (n=2694 post-quality control), no polymorphism in the HLA region was found to reach the genome-wide significance level or suggestive threshold in the discovery cohort with the outcome of 'any food allergy' (17) (Table 1). When analysed for specific food allergy such as peanut, egg and milk allergy, two polymorphisms (non-synonymous mutation rs7192 of HLA-DRA and rs9275596 intergenic SNP between HLA-DQB1 and HLA-DQA2) were associated with an increased risk of peanut allergy only, and these findings were replicated in an independent cohort. However, this association was only observed in children of European ancestry and not non-European ancestry. These variants, rs7192 (r^2 = 0.25) and rs9275596 (r^2 = 0.48) were found to be in linkage disequilibrium with a 3' UTR variant, rs9273440 of HLA-DQB1, which was significantly associated with peanut allergy in another GWAS of food allergy (19).

Association with broad allele groups

Six of the nine studies that investigated *HLA* found associations with broad allele groups. With the exception of Savihlati et al who focused on cow's milk allergy (45), the remaining five studies investigated *HLA* in relation to peanut allergy (20, 27, 28, 34, 35). Savilahti et al did not find any significant associations with cow's milk allergy for HLA class II DR and DQ haplotypes (45). Meanwhile, Howell et al reported an amino acid variant (DRB1*08/12 - tyr16) and two alleles (DRB1*08, DQB1*04) that showed an increased proportion in peanut allergic individuals compared to controls, even after multiple testing correction (27). Two other allele groups, DQB1*02 and DQB1*05 were lower in peanut allergy cases compared to controls (28). Analysis of specific HLA proteins in the same study found a higher frequency of DQB1*06:03P, but a decreased frequency of DQB1*03:02 and DQB1*05:01P in peanut allergy cases compared to controls (28). The letter 'P' added at the end of the allele represent alleles that share the same peptide binding domains (47).

Apart from the Howell et al and Madore et al studies, three other studies reported an association with peanut allergy, but these associations did not survive multiple testing adjustment (20, 34, 35) (Table 1). These studies had smaller sample sizes in comparison to

other studies which may have contributed to the lack of association. In Shreffler et al's study carried out in discordant sibling pairs, none of the alleles investigated were associated with peanut allergy in 73 cases (35). However, the DQ7 serotype frequency was higher in sibling controls than those with peanut allergy. In the other study of 84 cases, DRB1*13 and DQB1*06 alleles were higher in cases than controls (34). The last study found an association between reduced risk of peanut allergy and two amino acid variants, which were in linkage disequilibrium in the HLA-DRB1 gene (positions 37 and 71) (20). The association between peanut allergy and the variant at position 71 was initially discovered by Hong et al (17), but it did not remain significant in the replication cohort.

FLG

Similarly, the gene encoding filaggrin (*FLG*) was also commonly investigated with seven studies investigating association of different *FLG* variants with peanut, cow's milk or food allergy (19, 24, 25, 30, 38, 45, 46) and one study investigating the association in the presence of an environmental exposure (gene-environment interaction) (15). Similar to the studies on *HLA*, these studies tend to investigate different combinations of loss-of-function *FLG* mutations, making direct comparisons between the studies challenging. The combination of mutations investigated for each of these studies is shown in Table 1.

Six studies reported a significant association with either food allergy or peanut allergy in the presence/absence of environmental exposure (19, 24, 25, 30, 38, 46). Cases were reported to have a higher proportion of loss-of-function mutations (24, 30) and individuals with loss-of-function mutations (25, 30, 38, 46) or 'T' allele of intron variant, rs12123821 (19) were at least two times more likely to have food or peanut allergy than the control group. However, in a birth cohort study where participants were followed up prospectively for 18 years, an association between food allergy and *FLG* mutations was only observed at 10 and 18 years but not at younger ages (at 1, 2 and 4 years old) (46). It may be that *FLG* mutations are less strongly associated with food allergies that predominate in younger children, such as egg and milk.

The study on cow's milk allergy by Savilahti et al did not find any significant associations with cow's milk allergy for any of their investigated *FLG* polymorphisms (combined del22824, 501-C/T, R2447X, S3247, 3702delG) (45).

One of the identified studies, Brough et al, investigated effect modifications of genetic polymorphisms in *FLG* on the association between peanut allergy and peanut exposure (15).

In this study, 9% of all children (N=623) had a loss-of function *FLG* mutations (combined R501X, S3247X, R2447X, 2282del4, 3673delC and/or 3702delG) whereas in peanut allergy cases, 4 out of 20 (20%) carried the loss-of function *FLG* mutations. In the multivariate model, children with one or more *FLG* mutations had a 3.3 times increased odds of peanut allergy with each natural log (ln [log e]) unit increase in house dust peanut exposure. On the other hand, no association between peanut exposure and peanut allergy or peanut sensitisation was observed in children with the wild type *FLG* genotype.

CD14

Three small studies (N <200 subjects in each study) investigated the association of cluster of differentiation 14 (CD14) gene and food allergy (33, 36, 37). These studies all investigated the 5' UTR variant –159 C/T (rs2569190) but obtained conflicting results. Dreskin et al found the C allele to be associated with peanut allergy (33). Conversely, Woo et al (36) found a higher proportion of T alleles in food allergy cases than the controls in both codominant and dominant recessive models, while Campos et al (37) found no evidence of an association between this polymorphism and food allergy. However, it is worth noting that the two latter studies were carried out in different populations – the Woo study predominantly Caucasian with some mixed ethnicity (African American or others not specified) while the Campos study was carried out in a Japanese population.

STAT6

Three studies investigated the associations between polymorphisms within gene encoding signal transducer and activator of transcription 6 (*STAT6*) and nut allergy (23), food allergy (38) or food-related anaphylaxis (40). The G allele of 3' UTR variant 2964G/A (rs324015) was found at an increased frequency in Caucasian children with nut allergy (23). This same variant, however, was not associated with food-related anaphylaxis in Japanese children (40). The last study on food allergy found an association with a 5' UTR variant in the STAT6 region, rs167769 (38), which was previously associated with eosinophilic esophagitis (48).

IL10

Chen et al (41) and Jacob et al (42) investigated variants at the gene encoding interleukin 10 (*IL10*) in relation to any food and cow's milk allergy, respectively. A common SNP investigated by both studies is the -1082 A/G (rs1800896) variant, a 2 kilo base pair (kb) upstream variant. Jacob et al found that the GG allele for -1082 A/G (rs1800896) was more common in the cow's milk allergy group than the control group (42). Moreover, the *IL10* -

3575A, *IL10* -2849A, *IL10* -2763C, *IL10* -1082G and *IL10* -592C haplotype was also higher in cases (10%) than controls (2%). On the other hand, Chen et al did not find an association of any food allergy (milk inclusive) with either the same variant -1082 A/G (rs1800896) or -592 A/C (rs1800872) variant (41).

IL13

Two studies found an association between food allergy and interleukin 13 (*IL13*) intron variant, rs1295686 (32, 38). Both studies observed an increased risk of food allergy among those with the risk allele (A/T). Interestingly, the studies were carried out in different populations, with the Ashley et al (32) study conducted in a Caucasian population using a tag-SNP selection approach, while the Hirota et al (38) study was done in a Japanese population investigating genes previously associated with atopic dermatitis and/or eosinophilic esophagitis.

C11orf30/LRRC32

Hirota et al (38) investigated the association of food allergy with 26 genes previously associated with atopic diseases and eosinophilic esophagitis in GWAS. In this study, a locus within the chromosome 11 open reading frame 30/ leucine-rich repeat-containing protein 32 (*C11orf30)/LRRC32)* region was one of 14 loci found to be associated with food allergy at the nominal level ($p<0.05$). rs11236809, a 500 base pair downstream variant, was associated with food allergy. In another study by Marenholz et al, an intergenic variant (rs2212434) within the same *C11orf30/LRRC32* region was also associated with food allergy in the discovery cohort and two independent replication cohorts (19). Additionally, Asai et al (21) found an association between peanut allergy and rs7936434, a variant 30kb from *C11orf30*. Collectively, these three studies point towards the association of the region with food or peanut allergy but none investigated the same SNPs for comparison.

Other genes

There were several other studies that investigated genetic associations with food allergy, namely *NLRP3 (39), FcyRIIa (29), IDO(43), NAT2 (26), SPINK5 (31), IL28B (IFNL3) (22), SERPINB (19), TGFb1(42), TLR2* and *TLR4 (44).*

NLRP3 was not found to be associated with food allergy, however, some of the investigated SNPs were found to be associated with food-related anaphylaxis (39).

NAT2, SERPINB and *SPINK5* were reported to be associated with food allergy in a single study each, while the remaining studies of the other genes found no association. Of particular significance is the *SERPINB* gene cluster, a newly identified region associated with challenge-proven food allergy. The association was identified in a GWAS carried out using data from the German Genetics of Food Allergy Study (GOFA) (19). One of the SNPs located in the intron of *SERPINB*, rs12964116, did not remain significant after multiple testing correction in a GOFA replication cohort, but was associated with food allergy when investigated in a second independent replication cohort. Additionally, *SPINK5* variant rs9325071, which has been shown to decrease expression of SPINK5 in the skin, was associated with challenge-proven food allergy in both the discovery and replication cohorts (31).

In Li et al (18), CNVR in *ODZ3, CTNNA3, LUZP2, RBFOX1* and *MACROD2* were found to be associated with food allergy. The *CTNNA3* region was also associated with peanut allergy in another study, where intron variant, rs7475217, was associated with a reduction in the risk of peanut allergy (21).

Apart from these genes, the second gene-environment interaction study investigated polymorphisms of the vitamin D binding protein gene, *GC*, which were found to modify the association between vitamin D levels and food allergy (16). Vitamin D insufficiency (≤ 50 nM/L) at 1 year was associated with food allergy in infants with the GG genotype of rs7041, but not in those with GT or TT genotypes. However, the study did not examine for an association between *GC* and food allergy, independently of vitamin D levels.

DISCUSSION

This is the first review to systematically collate genetic association studies of food allergy. Overall, studies were of varied quality and reproducibility of findings for the same SNPs were minimal. This is not particularly surprising given genetic association studies in food allergy are still emerging. While a number of discovery studies did not include a replication phase, it is promising to notice that more recent studies are recognising the importance of replication in order to minimise publication of false-positive findings. With the exception of two studies published in 2016 (16, 43), the remaining eight studies published within the past three years all included a replication analysis. Most studies also included an appropriate adjustment for population heterogeneity in the form of a statistical adjustment, an exclusion of mixed/other ethnicities in their statistical analysis, inclusion of ancestry

informative markers as genetically inferred ancestry or was mentioned as a limitation of their study. However, several studies failed to address the need for any population adjustment. Assessment of population stratification is essential in genetic studies since any allelic or genotypic frequencies observed may be correlated with ethnicity and not the disease outcome. Apart from population stratification, multiple testing adjustment is also crucial since absence of multiple correction may lead to false positive associations with food allergy. However, 13 of the included studies did not adequately address this criteria.

In this review, we have included studies that have used an OFC as a diagnostic measure for defining food allergy as well as studies using measures of IgE sensitisation in conjunction with history of reaction. Out of the 32 included studies, 11 studies defined food allergy based on history of reactions and SPT, 9 used OFC and the remaining 12 studies used a combination of classifications – an OFC where possible/available and where unavailable, a history of reaction was used instead. Evidently, there is still a paucity of studies using OFC as a definition for food allergy. Use of SPT and history of reaction alone is likely to increase the chances of misclassification of food allergy cases.

Despite these limitations, reproducible associations with food allergy were found for a limited number of genes. The most reproducible association with food allergy is for the *FLG* loss-of-function mutations, which was independently reported in eight studies. *FLG* encodes for an intermediate filament-associated protein that aggregates keratin intermediate filaments in mammalian epidermis which are important in water retention (49). A loss-of-function mutation in *FLG* would thus potentially increase skin permeability and enhance allergen penetration through the skin (50, 51). This mechanism has been demonstrated in several mouse model studies (52-54). *FLG* variants have also been shown to be associated with eczema and other allergic diseases (55). While there have been several studies investigating *FLG* association with food allergy, we were unable to perform a meta-analysis since only two studies investigated the same set of FLG polymorphisms. Studies of this gene often combine multiple loss-of-function mutations for analysis of association with disease. The combination of loss-of-function mutations investigated differs between studies, often based on the ethnicity of study participants. Nonetheless, currently available data overall support a genuine association between food allergy and *FLG*.

The next most reproducible associations were found between variants at HLA genes DQB1 and DRB1, and peanut allergy phenotypes. The HLA-DR and -DQ molecules are

expressed in several cells with antigen presenting capability such as B cells, macrophages and monocytes which are known to play a critical role in the development of allergy. One of the key steps to antigen-specific immune responses is antigen presentation by HLA molecules. As these HLA molecules have specific molecular polymorphisms confined to its peptide binding groove, these polymorphisms may alter the binding affinity of antigen presenting cells for specific peanut peptides (17). In particular, the polymorphic amino acid residue 71 along with position 13, 70 and 74, have been shown to affect the binding specificity of pocket 4, therefore influencing the presentation and interaction of peanut antigens (17, 56). Two SNPs in this region which were associated with peanut allergy, rs7192 and rs9275596, were additionally found to affect DNA methylation and thereby expression levels of HLA-DRB1 and HLA-DQB1 genes (17). The results of this review appear to show a distinction in genetic association based on the type of food. For instance, it is likely that HLA plays a causal role in food allergy, with high specificity to peanut allergy.

A recently identified gene, *C11orf30/LRRC32* has shown promising results for an association with food allergy. The C11orf30/LRRC32 region has previously been associated with eczema (57-59), asthma (60, 61), serum IgE levels (62) and eosinophilic esophagitis (48). The *C11orf30* encodes the EMSY protein which is responsible for binding of BRCA2 cancer susceptibility gene (63). Given its role in inflammatory diseases, *C11orf30* may play a role in epithelial barrier and differentiation (64). The neighbouring gene, *LRRC32*, is a surface biomarker expressed on regulatory T cells (65) shown to be important in immune tolerance (66). One of the investigated SNPs in this region, rs2212434, was associated with food allergy (19) and an association with eczema was previously identified in a large meta-GWAS on eczema (67). Another SNP in the region was also found to increase the risk of atopic march (rs2155219, 17 kb away from rs2212434) (68), further supporting the role of this region in allergic disease.

Collectively, the involvement of several genes in the mechanism of food allergy points towards the complex and multifactorial nature of food allergy. Like other allergic diseases, the genetic architecture of food allergy appears to involve several relatively common genetic variants of low penetrance and variable expressivity, although the role for rare deleterious mutations has not yet been explored. Some of the genes with evidence for association with food allergy have also been shown to be associated with other allergic diseases such as eczema, asthma and allergic rhinitis. Identifying genes uniquely associated with food allergy is therefore challenging. Some genetic variants may increase overall

susceptibility to atopy, such as those in *FCER1A, STAT6, IL13* (69, 70) which are associated with total serum IgE. While these variants can manifest as a number of allergic diseases as well as symptomatic and asymptomatic sensitisation to foods and aeroallergens, others such as those in *HLA* may be specifically associated with reactions to a particular food such as peanut. As such, it is important for future studies to clarify whether the intention is to focus on genetic risk factors specific to food allergy, including specific food allergies such as peanut allergy, or to investigate shared markers for allergic diseases.

Limitations of this systematic review

We restricted our systematic review to paediatric studies since the prevalence of food allergy is known to be the greatest in children compared to adults and the quality of case phenotyping at the population level is higher. We also did not include results of studies that have carried out computer mapping or pathway analyses to find causal food allergy genes. These studies may provide greater insight into other potentially relevant genes that have not been examined in genetic association studies and may be worth pursuing, but is beyond the scope of the review. Several papers (71-73) that were often quoted in narrative reviews as relevant to food allergy genetic associations were excluded from our systematic review. These studies were excluded primarily because they did not include a healthy control group in their study and/or only investigated genetic associations with regard to severity of food allergy and not the absence/presence of food allergy. We were also unable to carry out meta-analysis on the collated data due to the small number of studies of each locus and the fact that studies investigated different polymorphisms at these loci.

Conclusions

To date there is relatively strong evidence that food allergy is associated with genetic variants at *FLG, HLA, IL13*, as well as some evidence for other variants (*SPINK5, SERPINB, C11orf30*) that warrant further investigation. Although several studies reported promising data to support associations of genetic variants with food allergy, they were compromised by issues of inadequate sample size, absence of multiple testing correction and population stratification. Future investigations would benefit from having larger numbers to improve power and include replication cohorts to validate findings. Further functional research is also necessary to unravel the mechanisms of action of identified novel gene variants responsible for the observed associations.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

AUTHOR CONTRIBUTIONS

NS, JK and JE were responsible for developing the protocol, search strategy and risk of bias assessment. NS and YW reviewed all titles and abstracts for eligibility against a pre-determined set of inclusion criteria. NS reviewed the full text of potentially eligible papers and extracted data from the original papers, including carrying out the quality assessment of included studies. VS checked the accuracy and authenticity of data extracted. DM and KA contributed to the data analysis and interpretation of data. All authors contributed to the drafting and revising the article for intellectual content and approve the final version of the manuscript.

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Figure legends

Figure 1 Flowchart of literature search process according to PRISMA 2009 flow diagram.

Figure 2 Percentage of studies that meet each of the criteria in risk assessment.

Figure 3 Genes/gene regions that were investigated in more than one study and their associations with any type of food allergy. Studies were classified as showing an association if they are associated with any food allergy after multiple testing correction. This included studies that showed suggestive or marginal significant associations. P values used were those determined by each study.

Table 1 Summary of investigated genes in included studies

Genes of interest	Author	SNPs/CNVs/alleles	Study type	Outcome	OR (95% CI)	p-value[a]	Within-study replication[a b c]	Cross-study replication[d e f]
ABCB11	Hong, 2015 (17)	rs16823014	GWAS	Egg allergy	No ORs given	$4.4x10^{-6}$	N	
ARHGAP24	Asai, 2017 (21)	rs744597	GWAS - Meta analyses	Peanut allergy	0.61 (0.5-0.74)	$3.98x10^{-7}$		
ATP10A	Martino, 2017 (20)	rs17555239	GWAS	Peanut allergy	2.58	$3x10^{-5}$	OR= 0.79, p= 0.131	
BCAS1	Martino, 2017 (20)	rs11700330	GWAS	Peanut allergy	0.23	$3x10^{-6}$	N	
C11orf30/LRRC32	Marenholz, 2017 (19)	rs2212434	GWAS	Food allergy	1.29	3.4×10^{-4}	OR = 1.47, $p = 8.2 \times 10^{-5}$ (Replication 1) p=1.4 × 10−4 (Replication 2)	N
C11orf30/LRRC32	Hirota, 2017 (38)	rs11236809	Candidate gene	Food allergy	1.34 (1.14-1.59)	0.00056	OR= 1.33 (1.08-1.63), p=0.0096, Pcombined=0.000014	N
C11orf30/ LOC101928813	Asai, 2017 (21)	rs7936434	GWAS - Meta analyses	Peanut allergy	1.58 (1.32-1.9)	$5.17x10^{-7}$		
CCDC80	Hirota, 2017 (38)	rs12634229	Candidate gene	Food allergy	1.26 (1.08-1.46)	0.0039	OR=1.24 (1.02-1.52), p=0.030, Pcombined=0.00028	
CD14	Campos, 2007 (37)	CD14 -159 (rs2569190)	Candidate gene	Food allergy	No ORs given, only frequencies	0.8		✓(33, 36)
CD14	Campos, 2007 (37)	CD14 -550 (rs5744455)	Candidate gene	Food allergy	No ORs given, only frequencies	0.8		N
CD14	Dreskin, 2011 (33)	rs2569193	Candidate gene	Peanut allergy	1.33 (0.53–3.34)	0.54		N
CD14	Dreskin, 2011 (33)	rs2569190	Candidate gene	Peanut allergy	1.97 (1.02–3.79)	0.04		✓(36) X (37)
CD14	Woo, 2003 (36)	–159 C/T (rs2569190)	Candidate gene	Food allergy	1.7 (1.1-2.8)	0.03		✓(33) X (37)
CHCHD3 /EXOC4	Asai, 2017 (21)	rs78048444	GWAS	Peanut allergy	0.22 (0.12-0.39)	$5.44x10^{-7}$		

Genes of interest	Author	SNPs/CNVs/alleles	Study type	Outcome	OR (95% CI)	p-value[a]	Within-study replication[a b c]	Cross-study replication[d e f]
CLEC16A/DEXI	Hirota, 2017 (38)	rs2041733	Candidate gene	Food allergy	1.15(0.99-1.35)	0.074	OR=1.18 (0.96-1.45), p=0.12, Pcombined=0.019	
COG7	Hong, 2015 (17)	rs250585	GWAS	Egg allergy	No ORs given	$3.8x10^{-6}$	N	
CTNNA3	Asai, 2017 (21)	rs7475217	GWAS	Peanut allergy	1.64 (1.35-1.98)	$3.58x10^{-7}$		N
CTNNA3	Li, 2015 (18)	chr10:68282970-68284017 chr10:68383827-68407077	GWAS	Food allergy		0.0184	p=0.0206	N
EMCN	Hong, 2015 (17)	rs1318710	GWAS	Food allergy	No ORs given	$2.6x10^{-6}$	N	
FAM117A	Hong, 2015 (17)	rs9898058	GWAS	Milk allergy	No ORs given	$1.1 x10^{-6}$	N	
FcyRIIa	Pawlik, 2004 (29)	Not given	Candidate gene	Food allergy	No ORs given, only frequencies	None significant (p-values not given)		
FLG	Brown, 2011 (25)	Combined null genotype R501X and 2282del4	Candidate gene	Peanut allergy	English: 3.2 (1.4-7.2) English, Dutch, Irish: 5.3 (2.8-10.2)	0.0251 $3.0x\ 10^{-6}$	N	N
FLG	Brown, 2011 (25)	Combined null genotype R501X, 2282del4, R2447X, and S3247X	Candidate gene	Peanut allergy	Dutch: 3.5 (1.1-11.4) Irish: 3.3 (1.0-11.7)	0.0335 0.0640	OR=1.9 (1.4-2.6), P= $5.4 x 10^{-5}$	N
FLG	Hirota, 2017 (38)	rs6696556	Candidate gene	Food allergy	1.05 (0.84-1.31)	0.68	OR=1.15 (0.86-1.54), P=0.37, Pcombined=0.39	N
FLG	Hirota, 2017 (38)	p.S2889*	Candidate gene	Food allergy	2.32 (1.37-3.98)	0.001	Replication: OR=2.41 (1.27-4.49), p=0.0049 Combined: OR=2.36 (1.58-3.52), P=0.000015	N
FLG	Hirota, 2017 (38)	6 FLG null variants, c.3321delA, p.Q1701*, p.S2554*, p.S2889*, p.S3296*, and p.K4022*	Candidate gene	Food allergy	1.42 (1.04-1.92)	0.024	Replication: OR=2.04 (1.38-3.01), p=0.00035 Combined: OR=1.63 (1.28-2.07), P= 0.000055	N
FLG	Savilahti, 2010 (45)	5 filaggrin null mutations (del22824, 501-C/T,	Candidate gene	Cow's milk allergy	No ORs given, only frequencies	None significant (p>0.003)		✓(30, 46)

Genes of interest	Author	SNPs/CNVs/alleles	Study type	Outcome	OR (95% CI)	p-value[a]	Within-study replication[a b c]	Cross-study replication[d e f]
		R2447X, S3247, 3702delG)						
FLG	Venkataraman, 2014 (46)	5 polymorphisms (R501X, 2282del4, S3247X, 3702delG, and R2447X)	Candidate gene	Food allergy	10 years: 2.9 (1.2-7.0) 18 years: 2.5 (1.2- 5.3)	0.022 0.032		✓(30) X (45)
FLG	Brough, 2014 (15)*	Combined null mutations R501X, S3247X, R2447X, 2282del4, 3673delC and 3702delG	G x E	Peanut allergy	Univariate: 2.70 (0.9-8.0) Multivariate: 3.2 (1.1-9.8)	0.07 0.04		N
FLG	Tan, 2012 (30)	R501X, 2282del4, R2447X, S3247X, and 3702delG	Candidate gene	Food allergy	3.2 (1.2-8.5)	0.016 (0.055 after adjusting for eczema)		✓(46) X (45)
FLG	Asai, 2013 (24)	Combined rs61816761, rs41370446, rs138726443, rs150597413	Candidate gene	Peanut allergy	1.96 (1.49-2.58)	5.12×10^{-7}		N
FLG-AS1	Marenholz, 2017 (19)	rs12123821	GWAS	Food allergy	2.55	8.4×10^{-10}	OR=2.86, p= 6.1×10^{-7} (Replication 1)	N
FXR1	Martino, 2017 (20)	rs6763069	GWAS	Peanut allergy	0.38	2×10^{-5}	N	
GC	Koplin, 2016 (16)*	Combined rs7041 and rs4588	G x E	Food Allergy	6.0 (0.9-38.9)	Pinteraction= 0.014		
GLB1	Hirota, 2017 (38)	rs6780220	Candidate gene	Food allergy	1.40 (1.21-1.62)	0.0000082	OR=1.20 (0.99-1.45), p=0.064 Pcombined=0.0000025	
HLA	Martino, 2017 (20)	Amino acid polymorphisms at position 37	GWAS	Peanut allergy	0.3 (0.16-0.55)	9.8×10^{-5}	N	N
HLA	Martino, 2017 (20)	Amino acid polymorphisms at position 71	GWAS	Peanut allergy	0.34 (0.19-0.59)	1.5×10^{-4}	N	✓(17)
HLA	Savilahti, 2010 (45)	HLA class II haplotypes (DQB1, DRB1, DQA1)	Candidate gene	Cow's milk allergy	No ORs given, only frequencies	None significant (p>0.003)		N

Genes of interest	Author	SNPs/CNVs/alleles	Study type	Outcome	OR (95% CI)	p-value[a]	Within-study replication[a b c]	Cross-study replication[d e f]
HLA	Howell, 1998 (27)	DRB1*08	Candidate gene	Peanut allergy	No ORs given, only frequencies	0.0021 (Pcorrected=0.027)		N
HLA	Howell, 1998 (27)	DBR1*08/12 (tyr16)	Candidate gene	Peanut allergy	No ORs given, only frequencies	0.0023 (Pcorrected=0.029)		N
HLA	Howell, 1998 (27)	DQB1*04	Candidate gene	Peanut allergy	No ORs given, only frequencies	0.00042 (Pcorrected=0.0029)		N
HLA	Shreffler, 2006 (35)	DR11	Candidate gene	Peanut allergy	No ORs given, only frequencies	0.07 (Pcorrected=1.3)		N
HLA	Shreffler, 2006 (35)	DQ7	Candidate gene	Peanut allergy	No ORs given, only frequencies	0.04 (Pcorrected=0.3)		N
HLA	Shreffler, 2006 (35)	6 DQ serotypes (DQ2, DQ4, DQ5, DQ6, DQ8, and DQ9) and 17 DR allele groups (DR1, DR4, DR7, DR8, DR9, DR10, DR12, DR13, DR14, DR15, DR16, DR17, DR18, DR51, DR52, DR53, and DR103)	Candidate gene	Peanut allergy	No ORs given, only frequencies	None significant (P/Pcorrected>0.05)		N
HLA- DQB1	Madore, 2013 (28)	DQB1*06:03P	Candidate gene	Peanut allergy	2.59 (1.56–4.44)	1.6x 10-04, Pc=1.9x10^{-3}		N
HLA- DQB1	Madore, 2013 (28)	DQB1*02	Candidate gene	Peanut allergy	0.12 (0.07–0.21)	1.1 x 10-16, Pcorrected=1.3x10^{-15}		N
HLA- DQB1	Madore, 2013 (28)	DQB1*03:02P	Candidate gene	Peanut allergy	0.52 (0.34–0.79)	2.2 x10-03, Pcorrected=2.6x10^{-2}		N
HLA- DQB1	Madore, 2013 (28)	DQB1*05	Candidate gene	Peanut allergy	0.21 (0.08–0.50)	2.5 x10-04, Pcorrected=3.0x10^{-3}		N
HLA- DQB1	Madore, 2013 (28)	DQB1*05:01P	Candidate gene	Peanut allergy	0.25 (0.13–0.47)	7.7x 10-06,		N

Genes of interest	Author	SNPs/CNVs/alleles	Study type	Outcome	OR (95% CI)	p-value[a]	Within-study replication[a b c]	Cross-study replication[d e f]
						Pcorrected=$9.3x10^{-5}$		
HLA-A, B, DRB1, DQB1	Hand, 2004 (34)	B*07, DRB1*11	Candidate gene	Nut allergy	No ORs given, only frequencies	None significant (P>0.05)		N
HLA-A, B, DRB1, DQB1	Hand, 2004 (34)	DRB1*13	Candidate gene	Nut allergy	No ORs given, only frequencies	<0.05 (Pcorrected=0.82)		N
HLA-A, B, DRB1, DQB1	Hand, 2004 (34)	DQB1*06	Candidate gene	Nut allergy	No ORs given, only frequencies	<0.01 (Pcorrected=0.37)		N
HLA-B	Li, 2015 (18)	chr6:31300691-31304663	GWAS	Food allergy	Not given	Not given	p = 0.026 , Pcombined= 0.063	N
HLA-DQB1	Marenholz, 2017 (19)	rs9273440	GWAS	Peanut allergy	0.66	6.6×10^{-7}	OR=0.45, $p=3.8 \times 10^{-6}$ (Replication 1)	N
HLA-DQB1 and HLA-DQA2	Hong, 2015 (17)	rs9275596	GWAS	Peanut allergy	European: 1.7 (1.4-2.1) Non-European: 1.2 (0.8-1.8)	$6.8x10^{-10}$ 0.327	OR=1.7 (1.1-2.6), p=0.022 OR=0.6 (0.2-1.3), p=0.176	N
HLA-DRA	Hong, 2015 (17)	rs7192	GWAS	Peanut allergy	European: 1.7 (1.4-2.1) Non-European: 1.2 (0.8-1.8)	$5.5x10^{-8}$ 0.198	OR=1.8 (1.2-2.7), p=0.005 1.4 (0.7-3.1), p=0.375	N
HMGA2|LLPH	Hong, 2015 (17)	rs10878354	GWAS	Peanut allergy	Not given	$5.1x10^{-6}$	N	
IDO1 and IDO2	Buyuktiryaki, 2016 (43)	10 SNPs: rs3808606, rs3824259, rs10089084, rs6991530, rs10504013 rs11992749, rs10109853, rs4503083, rs2955903, rs7820268	Candidate gene	Food allergy	No ORs given, only frequencies	None significant (P values >0.05)		
IER5L	Martino, 2017 (20)	rs4240433	GWAS	Peanut allergy	3.61	$7x10^{-6}$	OR=0.83, 0.316	
IL10	Abe Jacob, 2013 (42)	IL10 -1082	Candidate gene	Cow's milk allergy	No ORs given, only frequencies	0.027 (Pcorrected= 0.054)		X (41)

Genes of interest	Author	SNPs/CNVs/alleles	Study type	Outcome	OR (95% CI)	p-value[a]	Within-study replication[a b c]	Cross-study replication[d e f]
IL10	Chen, 2012 (41)	-1082 A/G (rs1800896) and -592 A/C (rs1800872)	Candidate gene	Food allergy	No ORs given, only frequencies	0.994 0.770		✓(42)
IL13	Ashley, 2017 (32)	rs1295686	Candidate gene	Food allergy	1.75 (1.20-2.53)	0.003	OR=1.37 (1.03-1.82), p=0.03	
KIF3A/IL13	Hirota, 2017 (38)	rs1295686	Candidate gene	Food allergy	1.44 (1.23-1.68)	0.0000031	OR=1.34 (1.10-1.64), p=0.0038, Pcombined=0.000000067	
IL2/IL21	Hirota, 2017 (38)	rs17389644	Candidate gene	Food allergy	1.14(0.90-1.44)	0.28	OR=1.49 (1.13-1.97), p=0.0049, Pcombined=0.0096	
IL26	Martino, 2017 (20)	rs7300806	GWAS	Peanut allergy	0.28	$1x10^{-5}$	OR=0.82, p= 0.319	
IL28B	Gaudieri, 2012 (22)	rs12979860	Candidate gene	Food allergy	Cohort 1: 4.56 (1.7–12.6) Cohort 2: 3.0 (1.8–5.2)	0.004 0.04		
IL4/KIF3A	Marenholz, 2017 (19)	rs11949166	GWAS	Food allergy	0.6	1.2×10^{-13}	OR=0.69, $p=3.0 \times 10^{-5}$ (Replication 1)	
IMPAD1|LOC286177	Hong, 2015 (17)	rs7833294	GWAS	Milk allergy	No ORs given	$7.3x10^{-6}$	N	
ITIH5L	Hong, 2015 (17)	rs5961136	GWAS	Egg allergy	No ORs given	$2.4x10^{-6}$	N	
LINGO2	Martino, 2017 (20)	rs10812871	GWAS	Peanut allergy	0.38	$4x10^{-5}$	OR=0.68 p=0.014*	
LMX1A	Martino, 2017 (20)	rs6686894	GWAS	Peanut allergy	0.06	$4x10^{-7}$	OR=1.29, p=0.280	
LOC100129104|ZFAT	Hong, 2015 (17)	rs4584173	GWAS	Peanut allergy	No ORs given	$3.6x10^{-6}$	N	
LOC100289292|ETAA1	Hong, 2015 (17)	rs17032597	GWAS	Milk allergy	No ORs given	$1.6x10^{-6}$	N	
LOC100289677|TP53TG1	Hong, 2015 (17)	rs6942407	GWAS	Food allergy	No ORs given	$8.2x10^{-6}$	N	
LOC645314|SLC39A10	Hong, 2015 (17)	rs777717	GWAS	Food allergy	No ORs given	$4.7x10^{-6}$	N	
LOC729993|ERCC4	Hong, 2015 (17)	rs6498482	GWAS	Egg allergy	No ORs given	$4.8x10^{-6}$	N	
LSP1	Hong, 2015 (17)	rs78405116	GWAS	Milk allergy	No ORs given	$1.7x10^{-6}$	N	
LUZP2	Li, 2015 (18)	chr11:2477896124783183 chr11:24412621-24551109	GWAS	Food allergy	No ORs given, only frequencies	0.0226	p=0.0153	
MACROD2	Li, 2015 (18)	chr20:1510419315126507 chr20:14713890-14727386	GWAS	Food allergy	No ORs given, only frequencies	$3.37 x10^{-3}$	$p=1.41 x10^{-3}$	

Genes of interest	Author	SNPs/CNVs/alleles	Study type	Outcome	OR (95% CI)	p-value[a]	Within-study replication[a b c]	Cross-study replication[d e f]
MDN1	Martino, 2017 (20)	rs9362681	GWAS	Peanut allergy	2.83	$1x10^{-5}$	OR=1.43, p=0.037*	
NAT2	Gawronska-Szklarz, 2001 (26)	NAT2*4 (fast acetylator), NAT2*5, NAT2*6, and NAT2*7 (slow acetylators)	Candidate gene	Food allergy	No ORs given, only frequencies	P <0.001		
NAV2	Martino, 2017 (20)	rs2439871	GWAS	Peanut allergy	0.38	$1x10^{-5}$	OR=0.94, p=0.723	
NLRP3	Hitomi, 2009 (39)	rs12079994	Candidate gene	Food-induced anaphylaxis	1.81 (1.09–2.99)	0.021		
NLRP3	Hitomi, 2009 (39)	rs4925650	Candidate gene	Food-induced anaphylaxis	1.77 (1.26–2.49)	0.00091		
NLRP3	Hitomi, 2009 (39)	rs3806265	Candidate gene	Food-induced anaphylaxis	1.71 (1.20–2.43)	0.0029		
NLRP3	Hitomi, 2009 (39)	rs4612666	Candidate gene	Food-induced anaphylaxis	1.81 (1.27–2.56)	0.00086		
NLRP3	Hitomi, 2009 (39)	rs10925026	Candidate gene	Food-induced anaphylaxis	1.53 (1.09–2.16)	0.013		
NLRP3	Hitomi, 2009 (39)	rs10754558	Candidate gene	Food-induced anaphylaxis	1.80 (1.28–2.54)	0.00068		
NLRP3	Hitomi, 2009 (39)	rs10733112	Candidate gene	Food-induced anaphylaxis	1.71 (1.21–2.40)	0.0021		
NLRP3	Hitomi, 2009 (39)	rs2027432, rs4925648, rs12048215, rs10754555, rs10925019, rs4925654, rs12565738, rs4378247	Candidate gene	Food allergy	No ORs given	None significant (p>0.05)		
ODZ3	Li, 2015 (18)	chr4:183271349183291465 chr4:183559306-183565618	GWAS	Food allergy	No ORs given, only frequencies	0.0116	0.018	
OR10A3/NLRP10	Hirota, 2017 (38)	rs878860	Candidate gene	Food allergy	1.10 (0.95-1.27)	0.21	OR=1.29 (1.07-1.57), p=0.01, Pcombined=0.01	

Genes of interest	Author	SNPs/CNVs/alleles	Study type	Outcome	OR (95% CI)	p-value[a]	Within-study replication[a b c]	Cross-study replication[d e f]
OVOL1	Hirota, 2017 (38)	rs593982	Candidate gene	Food allergy	1.23 (1.06-1.42)	0.0049	OR=1.04 (0.86-1.26), p=0.72, Pcombined=0.016	
PAFAH1B1	Martino, 2017 (20)	rs8077351	GWAS	Peanut allergy	0.05	$3x10^{-5}$	OR=1.07, p=0.820	
PAX2	Martino, 2017 (20)	rs6584390	GWAS	Peanut allergy	3.56	$4x10^{-5}$	OR=1.03, p=0.864	
PLAGL1	Martino, 2017 (20)	rs6928827	GWAS	Peanut allergy	13.98	$1x10^{-7}$	OR=0.77, p=0.292	
PTPN22	Savilahti, 2010 (45)	R620W (rs2476601)	Candidate gene	Cow's milk allergy	No ORs given, only frequencies	None significant (p-value > 0.003)		
PYROXD1	Martino, 2017 (20)	rs7131777	GWAS	Peanut allergy	2.55	$4x10^{-5}$	N	
RBFOX1	Li, 2015 (18)	chr16:71266297196046 chr16:6763216-6801846	GWAS	Food allergy	No ORs given, only frequencies	$4.72x10^{-3}$	0.9989	
RGS21	Martino, 2017 (20)	rs12142904	GWAS	Peanut allergy	3.51	$5x10^{-6}$	OR=1.02, p=0.905	
RHOBTB1	Hong, 2015 (17)	rs10994607	GWAS	Food allergy	No ORs given	7.1x10-6	N	
RHOBTB1|TMEM26	Hong, 2015 (17)	rs10994613	GWAS	Milk allergy	No ORs given	4.8x10-6	N	
RIMS2	Martino, 2017 (20)	rs16870788	GWAS	Peanut allergy	3.58	$3x10^{-5}$	OR=0.93, p=0.734	
RNF130	Martino, 2017 (20)	rs864481	GWAS	Peanut allergy	2.91	$5x10^{-5}$	OR=1.09, p=0.681	
SALL3	Martino, 2017 (20)	rs73971133	GWAS	Peanut allergy	0.07	$3x10^{-5}$	OR=0.87, p=0.723	
SERPINB7	Marenholz, 2017 (19)	rs12964116	GWAS	Food allergy	1.9	5.7×10^{-6}	OR=1.69, $p=9.4 \times 10^{-3}$ (Replication 1) p=0.010 (Replication 2)	
SERPINB7/B2	Marenholz, 2017 (19)	rs1243064	GWAS	Hen's egg allergy	1.65	1.6×10^{-7}	OR=1.21, p=0.028 (Replication 1) p=0.15 (Replication 2)	
SGCD	Hong, 2015 (17)	rs7717393	GWAS	Egg allergy	No ORs given	$1.4x10^{-6}$	N	
SKAP1	Asai, 2017 (18)	rs16955960	GWAS	Peanut allergy	2.06 (1.54-2.75)	$1.01x10^{-6}$		
SLC2A9	Martino, 2017 (20)	rs10018666	GWAS	Peanut allergy	5.9	4×10^{-8}	OR=1.18, p=0.360	
SORBS2	Martino, 2017 (20)	rs57144668	GWAS	Peanut allergy	0.37	$3x10^{-5}$	OR=1.50, p=0.014*	

Genes of interest	Author	SNPs/CNVs/alleles	Study type	Outcome	OR (95% CI)	p-value[a]	Within-study replication[a b c]	Cross-study replication[d e f]
SPINK5	Ashley, 2017 (31)	77 tag-SNPs within a region of ~263 kb capturing 387 alleles with LD of r2≥.8	Candidate gene	Food allergy	2.95 (1.49-5.83)	0.001	OR=1.58 (1.13-2.20), p=0.007	
SSBP3|ACOT11	Hong, 2015 (17)	rs12121623	GWAS	Food allergy	No ORs given	$3.1x10^{-7}$	N	
STAT6	Tamura, 2003 (40)	G2964A (rs324015)	Candidate gene	Food-related anaphylaxis	No ORs given, only frequencies	0.4974		✓(23)
STAT6	Amoli, 2002 (23)	2964 G/A 3'UTR (rs324015)	Candidate gene	Nut allergy	2.9 (1.7– 4.9)	< 0.0001		X (40)
STAT6	Hirota, 2017 (38)	rs167769	Candidate gene	Food allergy	1.26 (1.06-1.50)	0.0082	OR=1.24 (0.99-1.56), p=0.06, Pcombined=0.0014	N
STXBP6|NOVA1	Hong, 2015 (17)	rs862942	GWAS	Peanut allergy	No ORs given	$3.0x10^{-6}$	N	
SV2C	Martino, 2017 (20)	rs10474468	GWAS	Peanut allergy	0.37	$5x10^{-5}$	OR=0.84, p=0.261	
TES	Martino, 2017 (20)	rs73220497	GWAS	Peanut allergy	0.06	$3x10^{-5}$	OR=1.04, p=0.891	
TGFb1	Abe Jacob, 2013 (42)	TGFb1 -509C/T	Candidate gene	Cow's milk allergy	No ORs given, only frequencies	0.6419		
TLR2	Galli, 2010 (44)	R753Q (rs5743708)	Candidate gene	Cow's milk and allergy	No ORs given, only frequencies	None significant (P values >0.05)		
TLR4	Galli, 2010 (44)	D299G (rs4986790)	Candidate gene	Cow's milk and allergy	No ORs given, only frequencies	None significant (P values >0.05)		
TMEM232/SLC25A46	Hirota, 2017 (38)	rs9326801	Candidate gene	Food allergy	1.33(1.09-1.61)	0.0037	OR= 0.98 (0.75-1.27), p=0.87, Pcombined=0.031	
TNFRSF6B/ZGPAT	Hirota, 2017 (38)	rs6010620	Candidate gene	Food allergy	1.11(0.95-1.29)	0.19	OR=1.19 (0.98-1.46), p=0.082, Pcombined=0.039	
TSLP/WDR36	Hirota, 2017 (38)	rs3806932	Candidate gene	Food allergy	1.19(1.02-1.40)	0.032	OR=1.15 (0.94-1.42), p=0.19, Pcombined=0.012	
ZNF365	Hirota, 2017 (38)	rs10995251	Candidate gene	Food allergy	1.32(1.14-1.53)	0.00017	OR=1.15 (0.95-1.39), p=0.18, Pcombined=0.00013	
ZNF652	Hirota, 2017 (38)	rs16948048	Candidate gene	Food allergy	1.20(0.97-1.47)	0.093	OR=1.41 (1.08-1.82), p=0.0096	

Genes of interest	Author	SNPs/CNVs/alleles	Study type	Outcome	OR (95% CI)	p-value[a]	Within-study replication[a b c]	Cross-study replication[d e f]
							Pcombined=0.0039	

CNVs: Copy number variations; GWAS: Genome-wide association study; GxE: Gene-environment interaction studies; OR: odds ratios; SNPs: single nucleotide polymorphisms

[a]Pcombined refers to p-values obtained from the combination of discovery and replication cohort, as given in the respective studies. Pcorrected refers to p-vales after multiple testing correction

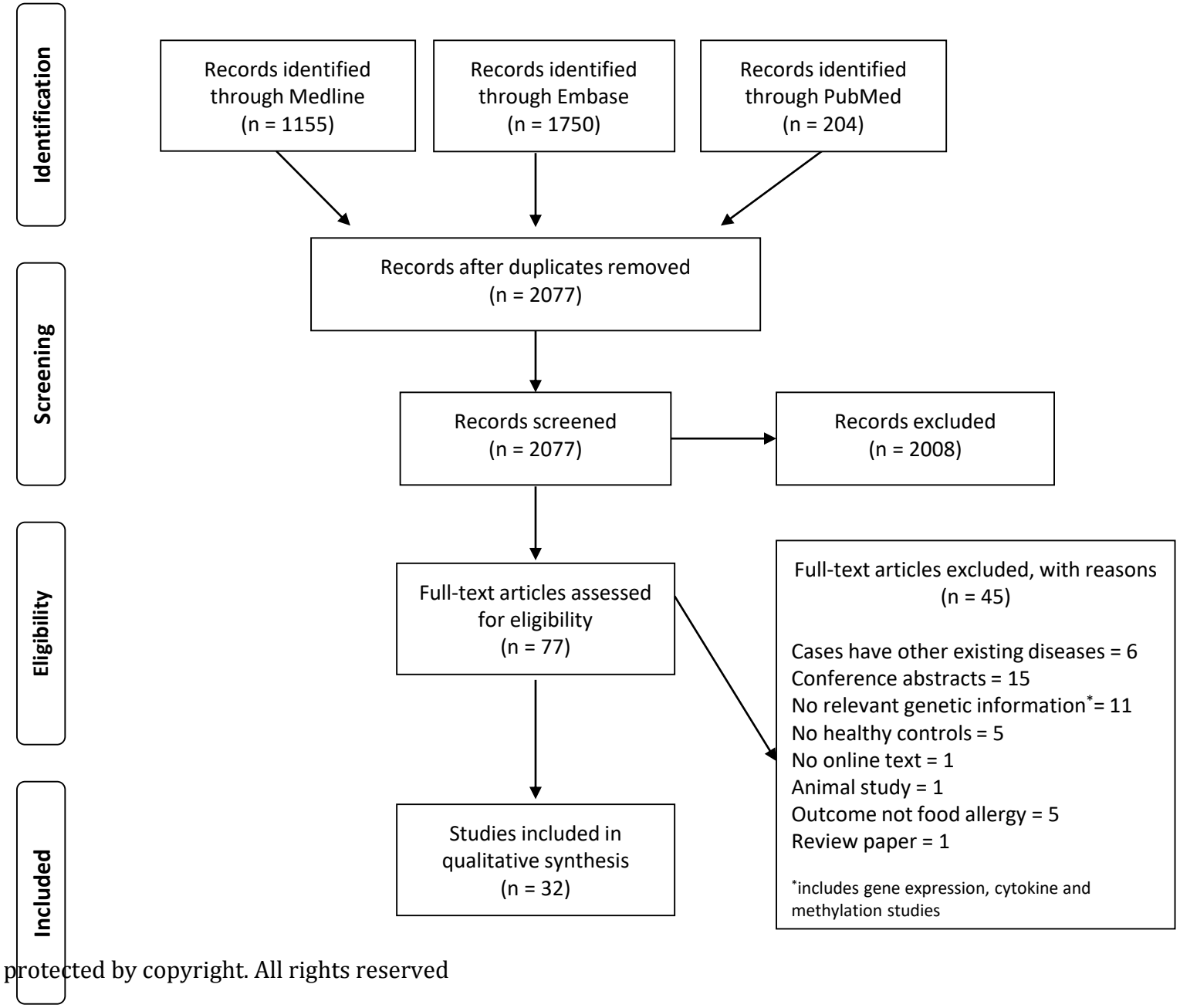
[b]Rows shaded grey indicate study did not include a replication cohort.

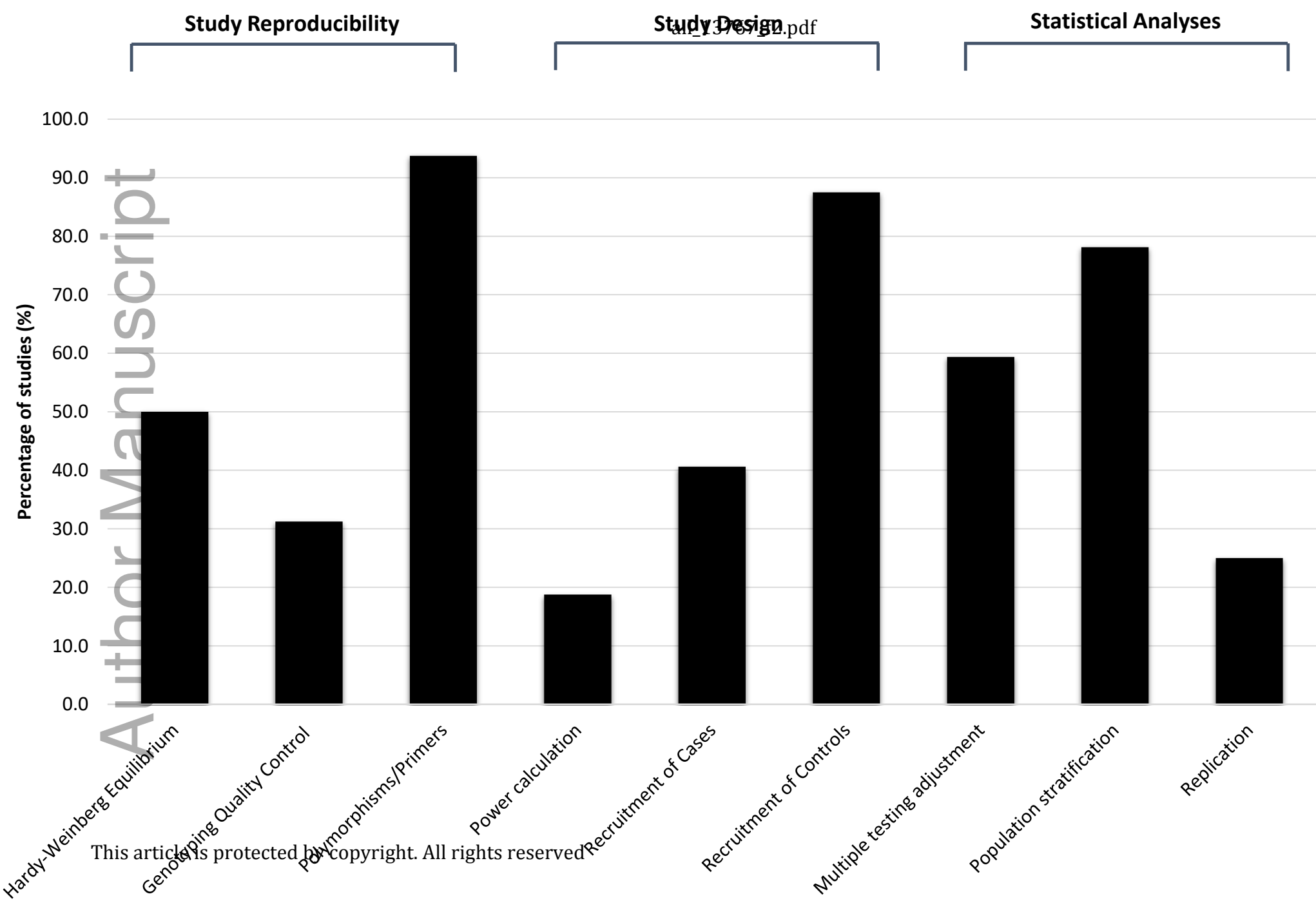
[c]N to denote studies have replication cohort but SNP/allele was not investigated in replication cohort.

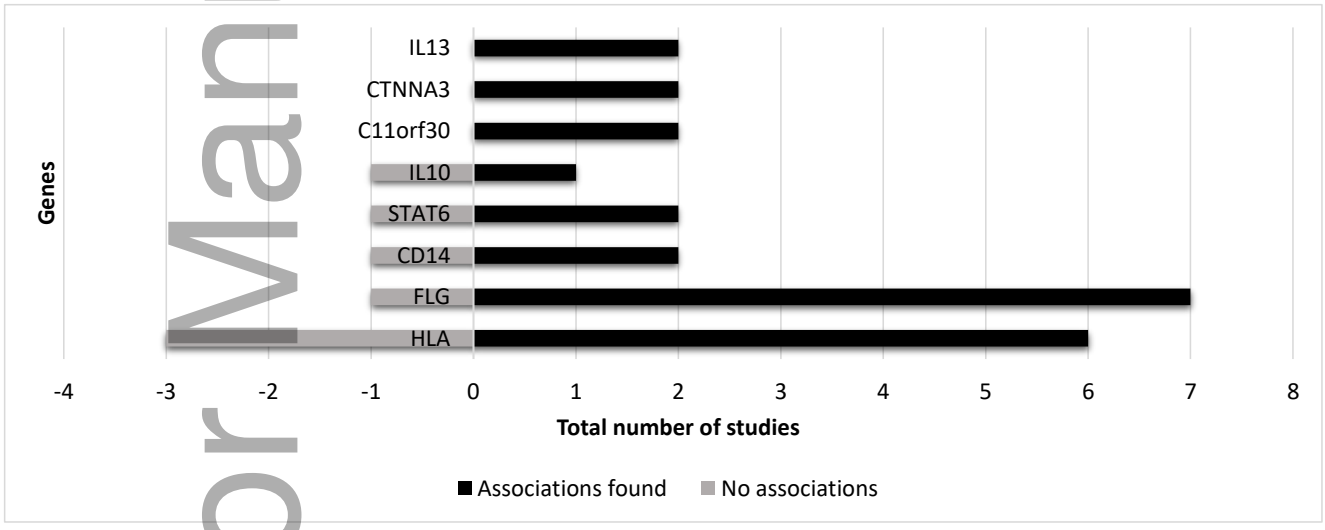
[d]Rows shaded grey indicate no other studies investigated same gene.

[e]N where there are other studies that investigated the same gene, but investigated SNP/allele differ among studies.

[f]✓indicate findings are associated with food allergy in cited study. X indicate findings are not associated with food allergy in cited study.







Author/s:
Suaini, NHA; Wang, Y; Soriano, VX; Martino, DJ; Allen, KJ; Ellis, JA; Koplin, JJ

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