

Genetic determinants of paediatric 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} 

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

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

³Telethon Kids Institute, University of Western Australia, Perth, Western Australia, Australia

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

⁵Institute of Inflammation and Repair, University of Manchester, Manchester, UK

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

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

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

Correspondence

Jennifer J. Koplin, Royal Children's Hospital, Murdoch Children's Research Institute, Parkville, Vic., Australia.

Email: jennifer.koplin@mcri.edu.au

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) on 9 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 nonatopic 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. Twenty-two 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* and *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.

KEYWORDS

food allergy, genetics, single nucleotide polymorphisms, systematic review

1 | 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%-35% of the observed individual differences in food-specific

Abbreviations: CNVR, Copy number variation region; CNVs, Copy number variations; GWAS, Genome-wide association study; SNP, Single nucleotide polymorphisms; UTR, Untranslated region.

IgE.⁴ Twin studies found that monozygotic twins recorded higher concordance rates for sensitization to peanut allergen than dizygotic twins.^{2,3} Sicherer et al³ found that the heritability estimate for peanut allergy was 82%-87%, 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 was to examine the evidence for the association between genetic polymorphisms and food allergy and identify areas that need further investigation.

2 | 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

2.1 | Search methods for identification of studies

We searched three databases: MEDLINE (Ovid), EMBASE (Ovid) and PubMed for references using MeSH terms and thesaurus/keywords on 9 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 to studies of children aged 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.

2.2 | Inclusion criteria of studies

2.2.1 | Type of studies

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

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

- The presence of unaffected nonatopic 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 variations (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, nonoriginal articles (comments, editorials and 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.

2.2.2 | 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 (a) oral food challenge or (b) a combination of positive skin prick test and/or specific IgE levels and information on history of food allergy.

2.3 | 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 associations¹³ 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.

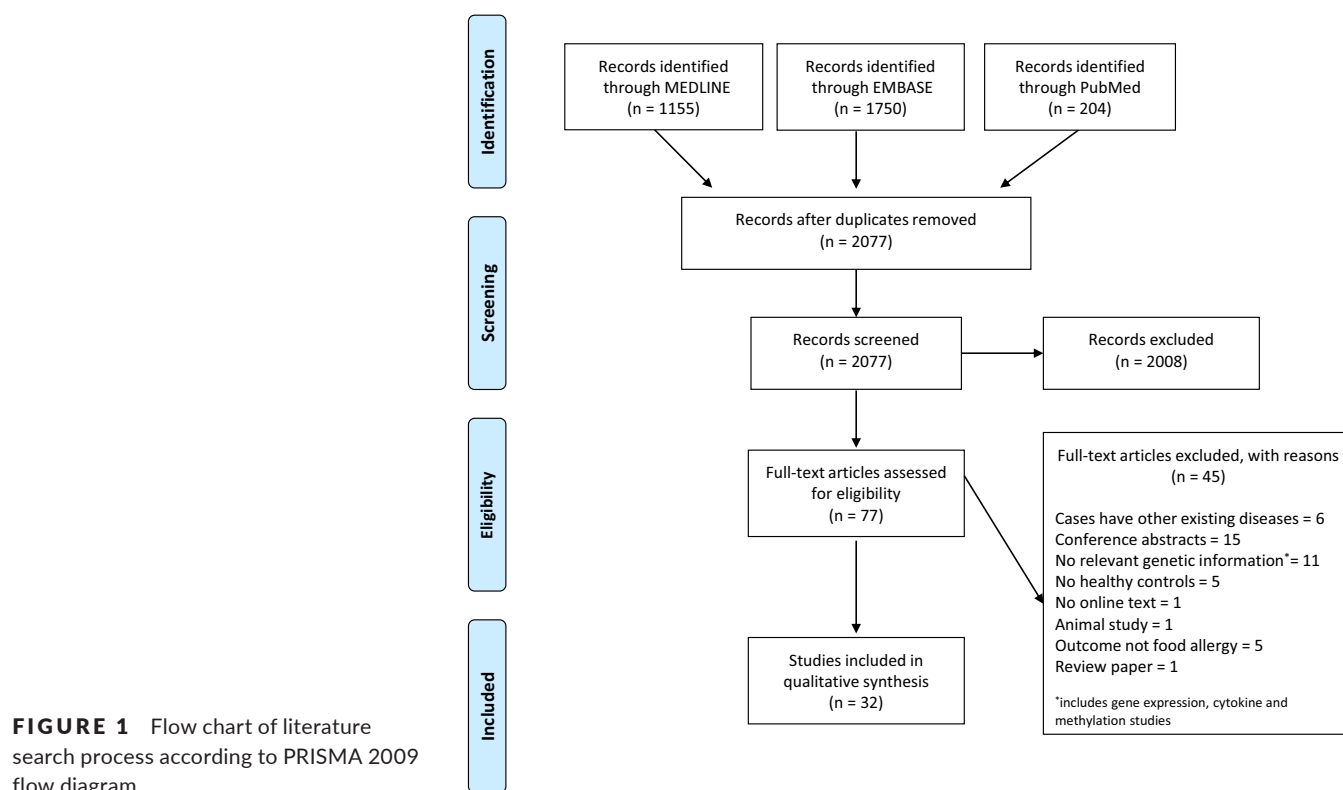


FIGURE 1 Flow chart of literature search process according to PRISMA 2009 flow diagram

2.4 | Data collection and synthesis

Two reviewers (NS and YW) independently screened the title and abstracts of all retrieved citations against the predetermined 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 were insufficient data to carry out pooled meta-analyses. In studies where several outcomes (eg asthma, eczema) were studied in addition to 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 nonatopic controls were used, only data pertaining to unaffected nonatopic controls were shown.

3 | RESULTS

3.1 | 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 1-93 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 nonallergic Caucasian controls,²² while the largest study was a GWAS with 2197 European subjects (671 with food allergy, 144 nonallergic nonsensitized controls and 1382 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" and "African American").^{15-18,20,31-36} Four others were carried out in Japanese populations,³⁷⁻⁴⁰ one was carried out in a Taiwanese population,⁴¹ and there were five studies where ethnicity was not mentioned.⁴²⁻⁴⁶

3.2 | Quality assessment

A detailed assessment of study quality can be found in the Online Repository Table S3. Seventeen of the included studies were of low

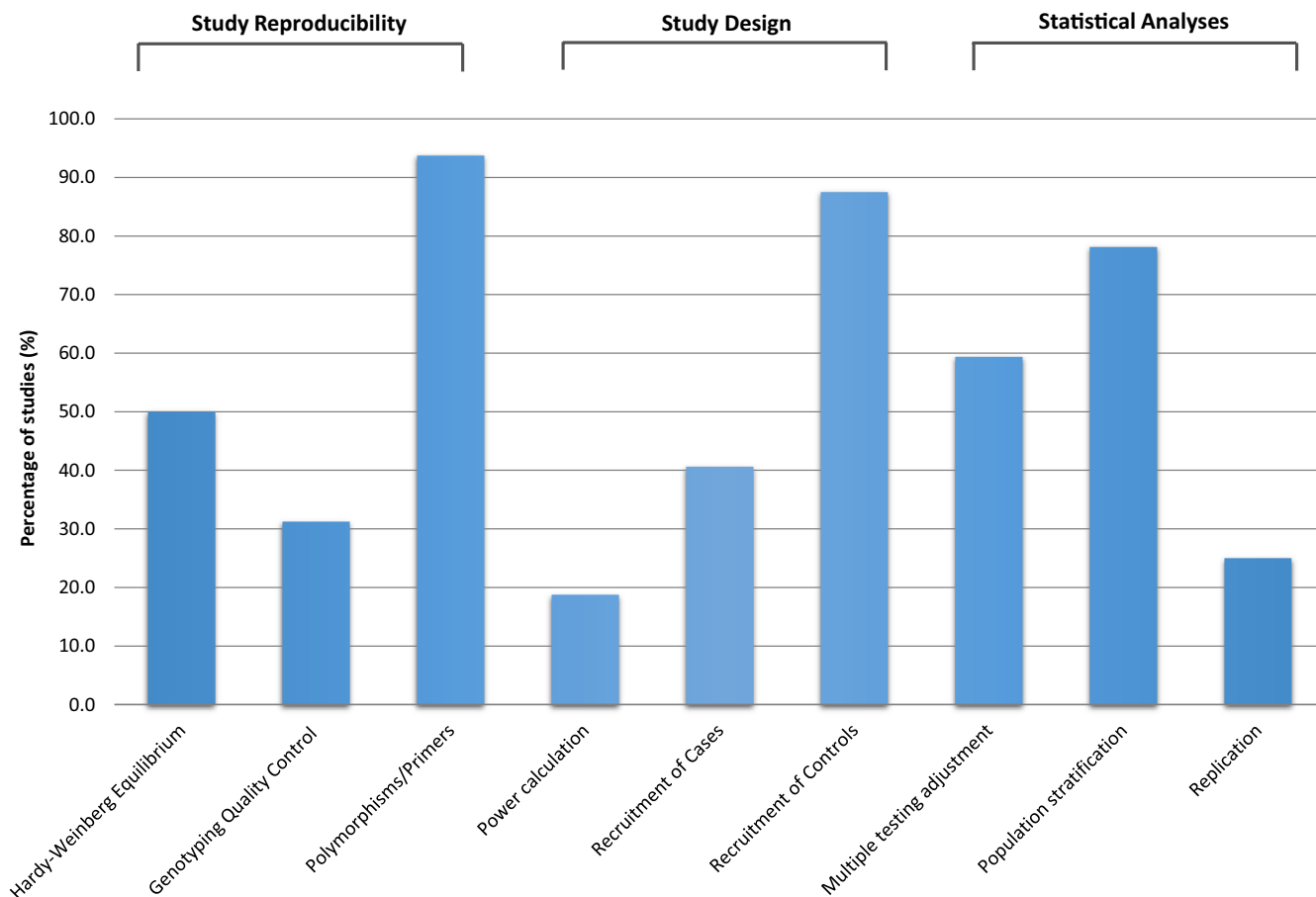


FIGURE 2 Percentage of studies that meet each of the criteria in risk of bias assessment

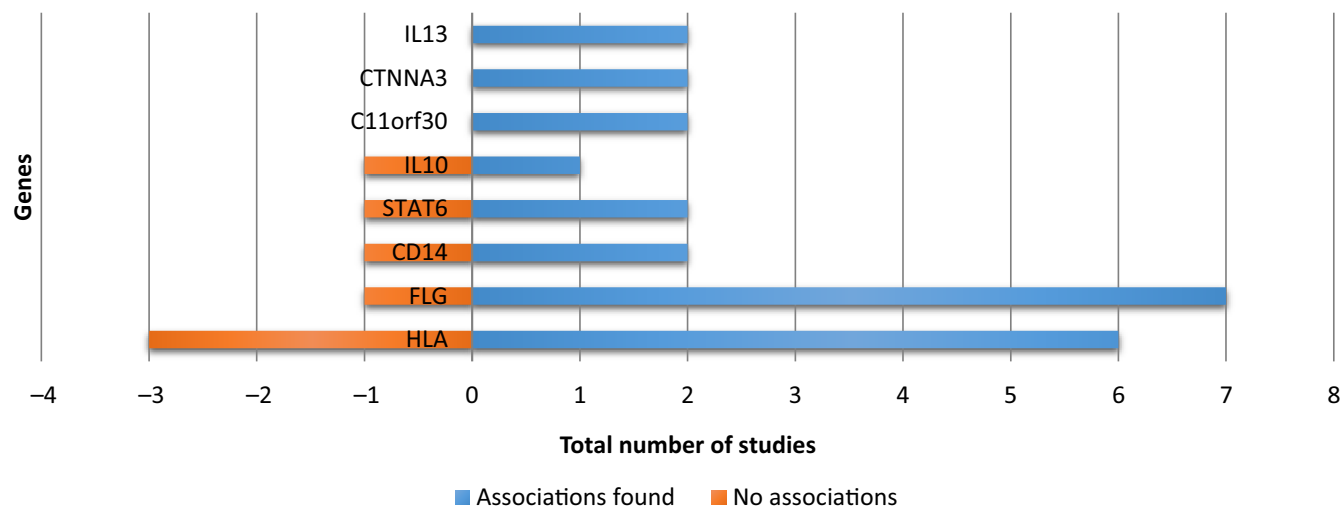


FIGURE 3 Genes/gene regions that were investigated in more than one study and their associations with any type of food allergy. Studies were classified as showing an association if they are associated with any food allergy after multiple testing correction. This included studies that showed suggestive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

quality, 10 were 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 these criteria as they restricted their analyses to one population group (Figure 2). Several studies carried out meta-analyses with additional

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	4.4×10^{-6}	N	
ARHGAP24	Asai, 2017 ²¹	rs744597	GWAS - Meta-analyses	Peanut allergy	0.61 (0.5-0.74)	3.98×10^{-7}		
ATP10A	Martino, 2017 ²⁰	rs17555239	GWAS	Peanut allergy	2.58	3×10^{-5}	OR = 0.79, P = 0.131	
BCAS1	Martino, 2017 ²⁰	rs11700330	GWAS	Peanut allergy	0.23	3×10^{-6}	N	
C11orf30/LRRC32	Marenholz, 2017 ¹⁹	rs2212434	GWAS	Food allergy	1.29	3.4×10^{-4}	OR = 1.47, P = 8.2×10^{-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, P _{combined} = 0.000014	N
C11orf30/ LOC101928813	Asai, 2017 ²¹	rs7936434	GWAS - Meta-analyses	Peanut allergy	1.58 (1.32-1.9)	5.17×10^{-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, P _{combined} = 0.00028	
CD14	Campos, 2007 ³⁷	-159 (rs2569190)	Candidate gene	Food allergy	No ORs given, only frequencies	0.8		✓ (33, 36)
CD14	Campos, 2007 ³⁷	-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)	5.44×10^{-7}		
CLEC16A/DEI	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, P _{combined} = 0.019	
COG7	Hong, 2015 ¹⁷	rs250585	GWAS	Egg allergy	No ORs given	3.8×10^{-6}	N	
CTNNA3	Asai, 2017 ²¹	rs7475217	GWAS	Peanut allergy	1.64 (1.35-1.98)	3.58×10^{-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	2.6×10^{-6}	N	
FAM117A	Hong, 2015 ¹⁷	rs9898058	GWAS	Cow's milk allergy	No ORs given	1.1×10^{-6}	N	

(Continues)

TABLE 1 (Continued)

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}
<i>FcγRIIIa</i>	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 3.0×10^{-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), $P = 5.4 \times 10^{-5}$	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), $P = 0.37$, $P_{\text{combined}} = 0.39$	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, R2447X, S3247 and 3702delG)	Candidate gene	Cow's milk allergy	No ORs given, only frequencies	None significant ($P > 0.003$)		✓ (30, 46)
FLG	Venkataraman, 2014 ⁴⁶	5 polymorphisms (R501X, 2282del4, S3247X, 3702delG and R2447X)	Candidate gene	Food allergy	10 y: 2.9 (1.2-7.0) 18 y: 2.5 (1.2-5.3)	0.022 0.032		✓ (30) ✗ (45)
FLG	Brough, 2014 ¹⁵	Combined null mutations R501X, S3247X, R2447X, 2282del4, 3673delC and 3702delG	GxE	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) ✗ (45)
FLG	Asai, 2013 ²⁴	Combined rs61816761, rs41370446, rs138726443 and rs150597413	Candidate gene	Peanut allergy	1.96 (1.49-2.58)	5.12×10^{-7}		N

(Continues)

TABLE 1 (Continued)

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}
FLG-AS1	Marenholz, 2017 ¹⁹	rs12123821	GWAS	Food allergy	2.55	8.4×10^{-10}	OR = 2.86, $P = 6.1 \times 10^{-7}$ (Replication 1)	N
FXR1	Martino, 2017 ²⁰	rs6763069	GWAS	Peanut allergy	0.38	2×10^{-5}	N	N
GC	Koplin, 2016 ¹⁶	Combined rs7041 and rs4588	GxE	Food Allergy	6.0 (0.9–38.9)	$P_{\text{interaction}} = 0.014$		
GLB1	Hirota, 2017 ³⁸	rs6780220	Candidate gene	Food allergy	1.40 (1.21–1.62)	0.0000082	OR = 1.20 (0.99–1.45), $P = 0.064$ $P_{\text{combined}} = 0.0000025$	N
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 and DQA1)	Candidate gene	Cow's milk allergy	No ORs given, only frequencies	None significant ($P > 0.003$)		N
HLA	Howell, 1998 ²⁷	DRB1*08	Candidate gene	Peanut allergy	No ORs given, only frequencies	0.0021 ($P_{\text{corrected}} = 0.027$)		N
HLA	Howell, 1998 ²⁷	DBR1*08/12 (tyr16)	Candidate gene	Peanut allergy	No ORs given, only frequencies	0.0023 ($P_{\text{corrected}} = 0.029$)		N
HLA	Howell, 1998 ²⁷	DQB1*04	Candidate gene	Peanut allergy	No ORs given, only frequencies	0.00042 ($P_{\text{corrected}} = 0.0029$)		N
HLA	Shreffler, 2006 ³⁵	DR11	Candidate gene	Peanut allergy	No ORs given, only frequencies	0.07 ($P_{\text{corrected}} = 1.3$)		N
HLA	Shreffler, 2006 ³⁵	DQ7	Candidate gene	Peanut allergy	No ORs given, only frequencies	0.04 ($P_{\text{corrected}} = 0.3$)		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 ($P/P_{\text{corrected}} > 0.05$)		N
HLA-DQB1	Madore, 2013 ²⁸	DQB1*06:03P	Candidate gene	Peanut allergy	2.59 (1.56–4.44)	1.6×10^{-4} , $P_c = 1.9 \times 10^{-3}$		N
HLA-DQB1	Madore, 2013 ²⁸	DQB1*02	Candidate gene	Peanut allergy	0.12 (0.07–0.21)	1.1×10^{-16} , $P_{\text{corrected}} = 1.3 \times 10^{-15}$		N
HLA-DQB1	Madore, 2013 ²⁸	DQB1*03:02P	Candidate gene	Peanut allergy	0.52 (0.34–0.79)	2.2×10^{-3} , $P_{\text{corrected}} = 2.6 \times 10^{-2}$		N
HLA-DQB1	Madore, 2013 ²⁸	DQB1*05	Candidate gene	Peanut allergy	0.21 (0.08–0.50)	2.5×10^{-4} , $P_{\text{corrected}} = 3.0 \times 10^{-3}$		N

(Continues)

TABLE 1 (Continued)

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-DQB1	Madore, 2013 ²⁸	DQB1*05:01P	Candidate gene	Peanut allergy	0.25 (0.13-0.47)	7.7×10^{-6} , $P_{\text{corrected}} = 9.3 \times 10^{-5}$		N
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 ($P_{\text{corrected}} = 0.82$)		N
HLA-A, B, DRB1, DQB1	Hand, 2004 ³⁴	DQB1*06	Candidate gene	Nut allergy	No ORs given, only frequencies	<0.01 ($P_{\text{corrected}} = 0.37$)		N
HLA-B	Li, 2015 ¹⁸	chr6:31300691-31304663	GWAS	Food allergy	Not given	Not given	$P = 0.026$, $P_{\text{combined}} = 0.063$	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)	6.8×10^{-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)	5.5×10^{-8} 0.198	$OR = 1.8$ (1.2-2.7), $P = 0.005$ $OR = 1.4$ (0.7-3.1), $P = 0.375$	N
HMG2/LLPH	Hong, 2015 ¹⁷	rs10878354	GWAS	Peanut allergy	Not given	5.1×10^{-6}	N	
IDO1 and IDO2	Buyuktiyaki, 2016 ⁴³	10 SNPs: rs3808606, rs3824259, rs10089084, rs6991530, rs10504013, rs11992749, rs10109853, rs4503083, rs2955903 and 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	7×10^{-6}	$OR = 0.83$, 0.316	
IL10	Abe Jacob, 2013 ⁴²	-1082	Candidate gene	Cow's milk allergy	No ORs given, only frequencies	0.027 ($P_{\text{corrected}} = 0.054$)		✗ (41)
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), $P = 0.0038$, $P_{\text{combined}} = 0.000000067$	

(Continues)

TABLE 1 (Continued)

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}
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, P _{combined} = 0.0096	
IL26	Martino, 2017 ²⁰	rs7300806	GWAS	Peanut allergy	0.28	1 × 10 ⁻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 × 10 ⁻⁵ (Replication 1)	
IMPAD1/LOC286177	Hong, 2015 ¹⁷	rs7833294	GWAS	Cow's milk allergy	No ORs given	7.3 × 10 ⁻⁶	N	
ITIH5L	Hong, 2015 ¹⁷	rs5961136	GWAS	Egg allergy	No ORs given	2.4 × 10 ⁻⁶	N	
LINGO2	Martino, 2017 ²⁰	rs10812871	GWAS	Peanut allergy	0.38	4 × 10 ⁻⁵	OR = 0.68 P = 0.014*	
LMX1A	Martino, 2017 ²⁰	rs6686894	GWAS	Peanut allergy	0.06	4 × 10 ⁻⁷	OR = 1.29, P = 0.280	
LOC100129104/ZFAT	Hong, 2015 ¹⁷	rs4584173	GWAS	Peanut allergy	No ORs given	3.6 × 10 ⁻⁶	N	
LOC100289292/ETAA1	Hong, 2015 ¹⁷	rs17032597	GWAS	Cow's milk allergy	No ORs given	1.6 × 10 ⁻⁶	N	
LOC100289677/TP53TG1	Hong, 2015 ¹⁷	rs6942407	GWAS	Food allergy	No ORs given	8.2 × 10 ⁻⁶	N	
LOC645314/SLC39A10	Hong, 2015 ¹⁷	rs777717	GWAS	Food allergy	No ORs given	4.7 × 10 ⁻⁶	N	
LOC729993/ERCC4	Hong, 2015 ¹⁷	rs6498482	GWAS	Egg allergy	No ORs given	4.8 × 10 ⁻⁶	N	
LSP1	Hong, 2015 ¹⁷	rs78405116	GWAS	Cow's milk allergy	No ORs given	1.7 × 10 ⁻⁶	N	
LUZP2	Li, 2015 ⁴⁸	chr11:2477896124783183 chr11:24412621-24551109	GWAS	Food allergy	No ORs given, only frequencies	0.0226	P = 0.0153	
MACROD2	Li, 2015 ⁴⁸	chr20:1510419315126507 chr20:14713890-14727386	GWAS	Food allergy	No ORs given, only frequencies	3.37 × 10 ⁻³	P = 1.41 × 10 ⁻³	
MDN1	Martino, 2017 ²⁰	rs9362681	GWAS	Peanut allergy	2.83	1 × 10 ⁻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	1 × 10 ⁻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		

(Continues)

TABLE 1 (Continued)

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}
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 and 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	P = 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, P _{combined} = 0.01	
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, P _{combined} = 0.016	
PAFAH1B1	Martino, 2017 ²⁰	rs8077351	GWAS	Peanut allergy	0.05	3 × 10 ⁻⁵	OR = 1.07, P = 0.820	
PAX2	Martino, 2017 ²⁰	rs6584390	GWAS	Peanut allergy	3.56	4 × 10 ⁻⁵	OR = 1.03, P = 0.864	
PLAGL1	Martino, 2017 ²⁰	rs6928827	GWAS	Peanut allergy	13.98	1 × 10 ⁻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	4 × 10 ⁻⁵	N	
RBFOX1	Li, 2015 ¹⁸	chr16:71266297196046 chr16:6763216-6801846	GWAS	Food allergy	No ORs given, only frequencies	4.72 × 10 ⁻³	P = 0.9989	
RGS21	Martino, 2017 ²⁰	rs12142904	GWAS	Peanut allergy	3.51	5 × 10 ⁻⁶	OR = 1.02, P = 0.905	
RHOBTB1	Hong, 2015 ¹⁷	rs10994607	GWAS	Food allergy	No ORs given	7.1 × 10 ⁻⁶	N	
RHOBTB1/TMEM26	Hong, 2015 ¹⁷	rs10994613	GWAS	Cow's milk allergy	No ORs given	4.8 × 10 ⁻⁶	N	
RIMS2	Martino, 2017 ²⁰	rs16870788	GWAS	Peanut allergy	3.58	3 × 10 ⁻⁵	OR = 0.93, P = 0.734	
RNF130	Martino, 2017 ²⁰	rs864481	GWAS	Peanut allergy	2.91	5 × 10 ⁻⁵	OR = 1.09, P = 0.681	
SALL3	Martino, 2017 ²⁰	rs73971133	GWAS	Peanut allergy	0.07	3 × 10 ⁻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 × 10 ⁻³ (Replication 1) P = 0.010 (Replication 2)	

(Continues)

TABLE 1 (Continued)

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}
SERPINB7/B2	Marenholz, 2017 ¹⁹	rs1243064	GWAS	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	1.4×10^{-6}	N	
SKAP1	Asai, 2017 ¹⁸	rs16955960	GWAS	Peanut allergy	2.06 (1.54-2.75)	1.01×10^{-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	3×10^{-5}	OR = 1.50, $P = 0.014$	
SPINK5	Ashley, 2017 ³¹	77 tag-SNPs within a region of ~263 kb capturing 387 alleles with LD of $r^2 \geq 0.8$	Candidate gene	Food allergy	2.95 (1.49-5.83)	0.001	OR = 1.58 (1.13-2.20), $P = 0.007$	
SSBP3/JACOT11	Hong, 2015 ¹⁷	rs12121623	GWAS	Food allergy	No ORs given	3.1×10^{-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), $P = 0.06$, $P_{\text{combined}} = 0.0014$	N
STXBP6/NOVA1	Hong, 2015 ¹⁷	rs862942	GWAS	Peanut allergy	No ORs given	3.0×10^{-6}	N	
SV2C	Martino, 2017 ²⁰	rs10474468	GWAS	Peanut allergy	0.37	5×10^{-5}	OR = 0.84, $P = 0.261$	
TES	Martino, 2017 ²⁰	rs73220497	GWAS	Peanut allergy	0.06	3×10^{-5}	OR = 1.04, $P = 0.891$	
TGFb1	Abe Jacob, 2013 ⁴²	-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 allergy	No ORs given, only frequencies	None significant (P values > 0.05)		
TLR4	Galli, 2010 ⁴⁴	D299G (rs4986790)	Candidate gene	Cow's milk 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), $P = 0.87$, $P_{\text{combined}} = 0.031$	
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), $P = 0.082$, $P_{\text{combined}} = 0.039$	
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), $P = 0.19$, $P_{\text{combined}} = 0.012$	

(Continues)

TABLE 1 (Continued)

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}
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, P _{combined} = 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 P _{combined} = 0.0039	

CNVs, copy number variations; GWAS, genome-wide association study; GxE, gene-environment interaction studies; OR, odds ratios; SNPs, single nucleotide polymorphisms.

^aP_{combined} refers to P-values obtained from the combination of discovery and replication cohort, as given in the respective studies. P_{corrected} refers to P-values after multiple testing correction.

^bEmpty rows indicate study did not include a replication cohort.

^cN denotes studies have replication cohort but SNP/allele was not investigated in replication cohort.

^dEmpty rows indicate no other studies investigated same gene.

^eN denotes studies that investigated the same gene, but the investigated SNP/allele differ among studies.

^f✓ Indicates findings are associated with food allergy in cited study. ✗ Indicates findings are not associated with food allergy in cited study.

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.

3.3 | 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.

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

Associations with SNPs

In the first GWAS of food allergy by Hong et al¹⁷ (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" (Table 1). When analysed for specific food allergy such as peanut, egg and milk allergy, two polymorphisms (nonsynonymous 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 (r² = 0.25) and rs9275596 (r² = 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 Savilahti et al⁴⁵ who focused on cow's milk allergy, the remaining five studies investigated *HLA* in relation to peanut allergy.^{20,27,28,34,35} Savilahti et al⁴⁵ did not find any significant associations with cow's milk allergy for *HLA* class II DR and DQ haplotypes. Meanwhile, Howell et al²⁷ 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. 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 represents 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 with other studies which may have contributed to the lack of association. In Shreffler et al's³⁵ study carried out in discordant sibling pairs, none of the alleles investigated were associated with peanut allergy in 73 cases. 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 *HLA-DRB1* (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.

3.3.2 | 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 al⁴⁵ 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 and 3702delG).

One of the identified studies, Brough et al,¹⁵ investigated effect modifications of genetic polymorphisms in *FLG* on the association between peanut allergy and peanut exposure. 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 sensitization was observed in children with the wild-type *FLG* genotype.

3.3.3 | 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 al³³ found the C allele to be associated with peanut allergy. Conversely, Woo et al³⁶ found a higher proportion of T alleles in food allergy cases than the controls in both codominant and dominant-recessive models, while Campos et al³⁷ 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 was carried out in predominantly Caucasian with some mixed ethnicity (African American or others not specified), while the Campos study was carried out in a Japanese population.

3.3.4 | STAT6

Three studies investigated the associations between polymorphisms within gene encoding signal transducer and activator of transcription 6 (STAT6) and nut allergy,²³ food allergy³⁸ 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

3.3.5 | IL10

Chen et al⁴¹ and Jacob et al⁴² 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 al⁴² found that the GG allele for -1082 A/G (rs1800896) was more common in the cow's milk allergy group than

the control group. Moreover, the *IL10* -3575A, *IL10* -2849A, *IL10* -2763C, *IL10* -1082G and *IL10* -592C haplotypes were also higher in cases (10%) than controls (2%). On the other hand, Chen et al⁴¹ 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.

3.3.6 | *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 al³² study conducted in a Caucasian population using a tag-SNP selection approach, while the Hirota et al³⁸ study was done in a Japanese population investigating genes previously associated with atopic dermatitis and/or eosinophilic esophagitis.

3.3.7 | *C11orf30/LRRC32*

Hirota et al³⁸ 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,¹⁹ 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. Additionally, Asai et al²¹ 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.

3.3.8 | Other genes

There were several other studies that investigated genetic associations with food allergy, namely *NLRP3*,³⁹ *FcγRIIa*,²⁹ *IDO*,⁴³ *NAT2*,²⁶ *SPINK5*,³¹ *IL28B (IFNL3)*,²² *SERPINB*,¹⁹ *TGFβ1*,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* was 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.

4 | 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 was 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 recognizing the importance of replication in order to minimize publication of false-positive findings. With the exception of two studies published in 2016,^{16,43} the remaining eight studies published within the past 3 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 and 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 the absence of multiple corrections may lead to false-positive associations with food allergy. However, 13 of the included studies did not adequately address these 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 sensitization 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 are 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 were 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 HLA-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 positions 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*.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 levels⁶² 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.⁵⁷ The neighbouring gene, *LRRC32*, is a surface biomarker expressed on regulatory T cells⁶⁴ shown to be important in immune tolerance.⁶⁵ 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.⁶⁶ Another SNP in the region was also found to increase the risk of atopic march (rs2155219, 17 kb away from rs2212434),⁶⁷ further supporting the role of this region in allergic diseases.

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* and *IL13*^{68,69} which are associated with total serum IgE. While these variants can manifest as a number of allergic diseases as well as symptomatic and asymptomatic sensitization 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.

4.1 | 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 papers⁷⁰⁻⁷² 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.

5 | CONCLUSIONS

To date, there is relatively strong evidence that food allergy is associated with genetic variants at *FLG*, *HLA* and *IL13*, as well as some

evidence for other variants (*SPINK5*, *SERPINB* and *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 predetermined 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 of the article for intellectual content and approved the final version of the manuscript.

ORCID

Yichao Wang  <https://orcid.org/0000-0002-1166-3796>

Katrina J. Allen  <https://orcid.org/0000-0002-1921-4493>

Jennifer J. Koplin  <https://orcid.org/0000-0002-7576-5142>

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Online Supplementary Information

Genetic determinants of paediatric 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:

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

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

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

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

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

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

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

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

Table S1 Search strategy for Medline (Ovid)

Table S2 Search strategy for Embase (Ovid)

PubMed search strategy

Risk of bias assessment criteria

Table S3 Risk of bias assessment of included studies

Table S4 Summary of included studies

Search Strategies

Table S1 Search strategy for Medline (Ovid)

No.	Search Query
1.	exp Food Hypersensitivity/
2.	((nut*1 or peanut* or cashew* or tree-nut or egg*1 or milk or shellfish or shell-fish or wheat or food or almond*) adj3 (allerg* or hypersensiti* or hyper-sensiti* or sensiti*)).tw,kf,hw.
3.	exp Genome-Wide Association Study/
4.	(gene*1 or genetic* or mutation* or polymorphism* or SNP* or allele* or genome or genomewide or genome-wide or GWAS).tw,kf,hw.
5.	exp Genes/
6.	exp Genetic Predisposition to Disease/ or exp Polymorphism, Single Nucleotide/
7.	(newborn* or neonat* or infan* or toddler* or girl or girls or boy or boys or pre-schooler* or preschooler* or child or children or childhood or adolescen* or pediatric* or paediatric* or youth* or teen or teens or teenage*).af.
8.	ge.fs.
9.	(1 or 2) and (3 or 4 or 5 or 6 or 8) and 7
10.	Limit 9 to English language

Table S2 Search strategy for Embase (Ovid)

No.	Search Query
1.	exp food allergy/
2.	((nut*1 or peanut* or cashew* or tree-nut or egg*1 or milk or shellfish or shell-fish or wheat or food or almond*) adj3 (allergy or allergies or allergic*1 or hypersensiti* or hyper-sensiti* or sensiti*)).tw,kw,hw.
3.	(gene*1 or genetic* or mutation* or polymorphism* or SNP* or allele* or genome or genomewide or genome-wide or GWAS).tw,kw,hw.
4.	exp gene/
5.	exp genome-wide association study/
6.	exp genetic predisposition/
7.	exp single nucleotide polymorphism/
8.	(newborn* or neonat* or infan* or toddler* or girl or girls or boy or boys or pre-schooler* or preschooler* or child or children or childhood or adolescen* or pediatric* or paediatric* or youth* or teen or teens or teenage*).af.
9.	(1 or 2) and (3 or 4 or 5 or 6 or 7) and 8
10.	limit 9 to english language

PubMed search strategy

("food allergy" OR "food allergies" OR "food sensitivity" OR "food sensitivities" OR "nut allergy" OR "nut allergies" OR "nut sensitivity" or "nut sensitivities" OR "peanut allergy" OR "peanut allergies" OR "peanut sensitivity" or "peanut sensitivities" OR "cashew allergy" OR "cashew allergies" OR "cashew sensitivity" OR "cashew sensitivities" OR "tree nut allergy" OR "tree nut allergies" OR "tree nut sensitivity" OR "tree nut sensitivities" OR "tree-nut allergy" OR "tree-nut allergies" OR "tree-nut sensitivity" OR "tree-nut sensitivities" OR "egg allergy" OR "egg allergies" OR "egg sensitivity" OR "egg sensitivities" OR "milk allergy" OR "milk allergies" OR "milk sensitivity" OR "milk sensitivities" OR "shellfish allergy" OR "shellfish allergies" OR "shellfish sensitivity" OR "shellfish sensitivities" OR "shell fish allergy" OR "shell fish allergies" OR "shell fish sensitivity" OR "shell fish sensitivities" OR "shell-fish allergy" OR "shell-fish allergies" OR "shell-fish sensitivity" OR "shell-fish sensitivities" OR "wheat allergy" OR "wheat allergies" OR "wheat sensitivity" OR "wheat sensitivities" OR "almond allergy" OR "almond allergies" OR "almond sensitivity" OR "almond sensitivities") AND (gene OR genes OR genetic* OR mutation* OR polymorphism* OR SNP OR SNPs OR allel* OR genome OR genomewide OR genome-wide OR "genome wide" OR GWAS) AND (newborn* OR baby OR babies OR neonat* OR infan* OR toddler* OR pre-schooler* OR preschooler* OR kindergarten OR boy OR boys OR girl OR girls OR child OR children OR childhood OR adolescen* OR pediatric* OR paediatric* OR youth* OR teen OR teens OR teenage*) AND (NOTNLM OR publisher[sb] OR inprocess[sb] OR pubmednotmedline[sb] OR indatareview[sb] OR pubstatusaheadofprint)

Risk of Bias Assessment Criteria

In total, 9 criteria were used to assess risk of bias in eligible studies. These criteria were modified from those formulated by two previous studies (1, 2). Eligible studies were scored based on criteria encompassing study reproducibility, study design and appropriate statistical analyses. Each criteria were scored 1 if present or sufficiently meeting the criteria and 0 if absent. The score for each criteria were summed, giving a maximum total score ranging from 7 to 11 as some of the studies were not scored in some criteria. These scores were then transformed to a 10-point scale for comparison across studies. Studies were then ranked low if they scored 0 to 4, moderate for scores of 5 to 7 and high if they scored 8 or more. The criteria used were as follows:

Study reproducibility

1. Hardy-Weinberg Equilibrium (1 point)

Studies were scored for this criteria if they tested for Hardy–Weinberg equilibrium (HWE), and excluded and/or identified SNPs that did not pass HWE. Studies were considered adequate regardless of whether the cut-off used for HWE assessment was defined or otherwise.

2. Genotyping Quality Control (1 point)

Studies were considered adequate if they provided details on genotyping methods or included a reference to an article which did. Studies would have to provide information on one of the following measures of quality control: duplicate genotyping, blind genotyping (performed genotyping whilst blind to the clinical status of the patient) and/or process of analysing genotyping calls.

3. Polymorphisms/Primers (1 point)

Studies provided reference numbers (rs numbers) or primer sequences. If not, a reference to a previous publication which included these details was cited.

Study design

4. Power calculation (1 point)

Studies were scored if power calculation was done as part of the study whether retrospectively or prospectively.

5. Recruitment of cases (1 point)

Cases were representative of the population. Population-based studies and birth cohorts were scored as adequate but studies of hospital-based participants failed to obtain a point. For genome wide association studies (GWAS), only the discovery cohort was assessed for this component.

6. Recruitment of controls (2 points)

Controls were considered adequate if they were obtained from the same population as cases (1 point). Additional point was given if studies provided sufficient details that enable ascertainment of non-atopic/unaffected status of the control group. For genome wide association studies (GWAS), only the discovery cohort was assessed for this component.

7. Quality of phenotype (1 point)

Acceptable studies scored 1 point if oral food challenge (OFC) was used to define food allergy. Studies which used a combination of classifications including OFC were not allocated a point. For instance, in some studies, certain participants were defined as food allergic based on OFC where available while others were ascertained by history of reaction in conjunction with measures of IgE sensitisation. These studies did not

Statistical analyses

8. Multiple testing adjustment (1 point)

Acceptable studies included multiple testing adjustments when two or more SNPs were studied. This category was marked not applicable if only a single polymorphism was analysed or if the study analysed SNPs as a binary variable, e.g. multiple SNPs at the same locus combined into ‘has mutation’ vs ‘no mutation’.

9. Population stratification (1 point)

Population stratification were considered present if one of the following conditions were met:

- Statistical adjustment for population stratification was made AND/OR
- An independent set of polymorphic markers such as ancestry informative markers (AIMs) were genotyped AND/OR
- Presence of a population control group which was either genotyped or used as a comparison analyses AND/OR
- Analyses carried out only in one population excluding participants of other populations (in studies that were carried out in several populations)

Where these were absent, studies would need to have demonstrated an effort to gather a homogeneous population. Studies carried out in a homogenous population were not scored for this criteria. Studies that addressed population issues as a limitation were marked as 1 for this component. If studies did not address ethnicity or issues surrounding population and made no attempt to deal with stratification, they would fail to obtain a point for this criteria.

10. Replication (1 point)

Adequate studies included an independent replication cohort to validate findings observed in discovery cohort.

Table S3 Risk of bias assessment of included studies

Author	Study Reproducibility			Statistical analyses			Study Design				Study Quality
	Hardy-Weinberg Equilibrium	Genotyping Quality Control	Polymorphisms/Primers	Multiple testing adjustment	Population stratification	Replication	Power calculation	Recruitment of Cases	Recruitment of Controls	Phenotype definition	
Abe Jacob, 2013 (3)	1	0	1	1	0	0	1	0	2	0	Moderate
Amoli, 2002 (4)	0	0	1	NA	NA	0	0	0	0	0	Low
Asai, 2013 (5)	0	0	1	NA	1	0	0	1	0	0	Low
Asai, 2017 (6)	1	1	1	1	1	0	0	1	1	0	Moderate
Ashley, 2017 (7)	1	1	1	0	1	1	0	1	2	1	High
Ashley, 2017 (8)	1	1	1	1	1	1	1	1	2	1	High
Brown, 2011 (9)	0	0	1	NA	0	1	0	1	2	1	Moderate
Buyuktiryaki, 2016 (10)	0	0	1	0	0	0	0	0	2	1	Low
Campos, 2007 (11)	1	0	1	0	NA	0	1	0	1	0	Low
Chen, 2012 (12)	1	0	1	0	NA	0	0	0	2	0	Low
Dreskin, (13)	1	0	1	0	1	0	0	0	2	0	Moderate
Galli, 2010 (14)	0	0	1	0	0	0	0	0	1	1	Low
Gaudieri, 2012 (15)	1	0	1	0	NA	0	0	1	2	0	Moderate

Gawronska-Szklarz, 2001 (16)	0	0	0	0	NA	0	0	0	2	1	Low
Hand, 2004 (17)	0	0	1	1	1	0	0	0	0	0	Low
Hirota, 2017 (18)	0	0	1	0	NA	1	0	0	1	0	Low
Hitomi, 2009 (19)	1	0	1	0	NA	0	1	0	1	0	Low
Hong, 2015 (20)	1	1	1	1	1	1	0	1	2	0	High
Howell, 1998 (21)	0	0	1	1	NA	0	0	0	0	0	Low
Li, 2015 (22)	0	1	1	1	1	1	0	0	2	0	Moderate
Madore, 2013 (23)	0	1	1	1	NA	0	0	0	1	0	Low
Marenholz, 2017 (24)	1	1	1	1	1	1	1	0	1	0	High
Martino, 2017 (25)	1	1	1	1	1	1	0	1	2	0	High
Pawlik, 2004 (26)	1	0	1	0	NA	0	0	0	1	1	Low
Savilahti, 2010 (27)	0	0	1	1	0	0	0	1	2	1	Moderate
Shreffler, 2006 (28)	0	0	1	1	0	0	1	0	2	0	Moderate
Tamura, 2003 (29)	0	0	1	1	NA	0	0	0	1	0	Low
Tan, 2012 (30)	0	0	1	0	NA	0	0	1	2	0	Low
Venkataraman, 2014	1	1	0	NA	0	0	0	1	2	0	Moderate

(31)											
Woo, 2003 (32)	1	0	1	NA	1	0	0	0	1	0	Low
Gene x Environment Interaction Studies											
Brough, 2014 (33)	0	0	1	NA	NA	0	0	1	2	0	Low
Koplin, 2016 (34)	1	1	1	0	1	0	0	1	2	1	Moderate

NA – not applicable. Criteria marked as NA were not scored for relevant studies as described in the online repository text.

Table S4 Summary of included studies

Author	Country	Ethnicity	Type of allergy	Definition of Cases		Participants - Cases (sample size, age mean $\pm$ SD)		Participants - Controls (sample size, age mean $\pm$ SD)		Type of genetic study	Genes/SNPs of interest	Quality Score
				Discovery cohort	Replication cohort	Discovery cohort	Replication cohort	Discovery cohort	Replication cohort			
Abe Jacob, 2013 (3)	Brazil	Not mentioned	Cow's milk allergy	OFC or History of reaction		50 children, aged ≥ 5 years		224 individuals, age not provided		Candidate gene studies (no replication cohort)	IL10: (-3575A/T, -2849A/G, -2763A/C, -1082G/A, -592C/A) TGFB1: (-509C/T)	Moderate
Amoli, 2002 (4)	UK	Caucasian	Nut allergy	History of reaction + SPT		71 children with age of onset of nut allergy: 9.7 ± 12.1 years		184 blood donors, age not provided		Candidate gene studies (no replication cohort)	STAT6: 2964 G/A 3'UTR	Low
Asai, 2013 (5)	Canada	Caucasian	Peanut allergy	OFC or History of reaction + SPT/sIgE + or SPT + sIgE		679 subjects, 9.3 ± 4.0 years, range 0 -21 years (Age on 1st Jan 2009) (N=663 after QC)		894 adults, 65.5 ± 10.2 , range 33-84 years (N=889 after QC) 268 newborns, 9.7 ± 0.5 years, range 7-10 years (N=267 after QC)		Candidate gene studies (no replication cohort)	FLG: rs61816761, rs41370446, rs138726443, rs150597413	Low
Asai, 2017 (8) ⁺	Canada, Australia	Self-identified	Peanut and food allergy	OFC or History of reaction +		987 cases, 12 ± 6 years, range: 1-63		987 controls, 49 ± 25 years,		GWAS	Genome-wide	Moderate

Author	Country	Ethnicity	Type of allergy	Definition of Cases		Participants - Cases (sample size, age mean $\pm$ SD)		Participants - Controls (sample size, age mean $\pm$ SD)		Type of genetic study	Genes/SNPs of interest	Quality Score
		caucasian		SPT/sIgE or SPT + sIgE		years (N=850 after quality control)		range 6-93 years (N=926 after quality control)				
Ashley, 2017 (7)	Australia	<u>Discovery:</u> Caucasian, Asian and mixed Asian-Caucasian	Food allergy	OFC + SPT	OFC or History of reaction + SPT/sIgE or 95% PPV	367 food allergy cases 12.7 $\pm$ 0.75 months, 199 food sensitized but tolerant cases 12.6 $\pm$ 0.68 months	36 food allergic cases from the Barwon Infant Study (BIS), and 57 food allergic cases from the Melbourne Atopic Cohort (MACs), 72 food allergic cases from the Peanut Allergen Threshold Study (PATS) and 38 food allergic cases from the Probiotic and Peanut Oral Immuno-	156 non-food allergic controls 12.6 $\pm$ 0.65 months	132 non-allergic controls (BIS) 198 non-allergic controls (MACs), 1.1 $\pm$ 0.1 years	Candidate gene studies (with replication cohort)	IL13, nine tag SNPs	High

Author	Country	Ethnicity	Type of allergy	Definition of Cases		Participants - Cases (sample size, age mean $\pm$ SD)		Participants - Controls (sample size, age mean $\pm$ SD)		Type of genetic study	Genes/SNPs of interest	Quality Score
							Therapy study (PPOIT), 4.1 $\pm$ 4.0 years					
Ashley, 2017 (8)	Australia	<u>Discovery:</u> Caucasian (n=503), Asian (n=74) or mixed Asian-Caucasian (n=145). <u>Replication:</u> 657 individuals to be of European descent, 217 of mixed European-Asian descent and 32 of Asian descent.	Food allergy	OFC + SPT	OFC or History of reaction + SPT/sIgE or 95% PPV	367 food-allergic, age at recruitment 12.7 $\pm$ 0.75 months	203 food-allergic children, 2.5 years	156 non-allergic controls, age at recruitment 12.6 $\pm$ 0.65 months	330 non-atopic controls, 2.5years	Candidate gene studies (with replication cohort)	SPINK5, Seventy-seven tag-SNPs	High
Brown, 2011 (9)	Canada, Ireland, Netherlands, UK	White	Peanut allergy	OFC	OFC or sIgE +/- SPT	71 cases, English: recruited at birth Dutch: range	390 cases, mean age 9.5 years (range 0-21 years)	1000 non-peanut sensitised controls recruited at birth	891 controls, mean age 57.5 years (range 23-77 years)	Candidate gene studies (with replication cohort)	FLG pooled English/Dutch/Irish case collection: combined null genotype of 2 mutations (R501X and	Moderate

Author	Country	Ethnicity	Type of allergy	Definition of Cases		Participants - Cases (sample size, age mean $\pm$ SD)		Participants - Controls (sample size, age mean $\pm$ SD)		Type of genetic study	Genes/SNPs of interest	Quality Score
						(mean) 3-14 years (7.5) Irish: range (mean) 1-18 (10.5)		6851 population controls, no age provided			2282del4)) Candian: 4 mutations (R501X, 2282del4, R2447X, and S3247X)	
Buyuktiryaki, 2016 (10)	Turkey	Not mentioned	Food allergy	OFC + History of reaction + SPT/sIgE		100 children, median (IQR): 3.2 (1.7–7.0) years (Genetic analyses on 90 children)		112 children, median (IQR): 4.0 (2.3–7.0) (Genetic analyses on 108 children)		Candidate gene studies (no replication cohort)	IDO1 and IDO2 genes: 10 SNPs, rs3808606, rs3824259, rs10089084, rs6991530, rs10504013, rs11992749, rs10109853, rs4503083, rs2955903, rs7820268	Low
Campos, 2007 (11)	Japan	Japanese	Food allergy	OFC or History of reaction		88 childhood patients, 7.1 $\pm$ 5.0 years		101 children age, 9.45 $\pm$ 1.5 years		Candidate gene studies (no replication cohort)	CD14:-159 and -550 polymorphisms	Low

Author	Country	Ethnicity	Type of allergy	Definition of Cases		Participants - Cases (sample size, age mean $\pm$ SD)		Participants - Controls (sample size, age mean $\pm$ SD)		Type of genetic study	Genes/SNPs of interest	Quality Score
Chen, 2012 (12) ⁺	Taiwan	Taiwanese	Food allergy	History of reaction + SPT/sIgE		37 patients, 8.06 $\pm$ 6.25 years (range 1-32 years)		52 controls, 17.85 $\pm$ 15.19 years (range 1-59 years)		Candidate gene studies (no replication cohort)	IL10: rs1800896 and rs1800872	Low
Dreskin, 2011 (13) ⁺	USA	All ethnicities, predominantly European descent (54/64)	Severe peanut allergy	OFC or sIgE or History of reaction + SPT		53 highly peanut allergic individuals, range 3-69 years		64 peanut-tolerant full-siblings, age not provided		Candidate gene studies (no replication cohort)	CD14: rs2569190 and rs2569193	Moderate
Galli, 2010 (14)	Italy	Not mentioned	Cow's milk allergy	OFC + SPT		159 children (102 with eczema and 57 with food allergy), ranging from 6-198 months, median 58 months		147 healthy controls, matched for age and sex		Candidate gene studies (no replication cohort)	TLR-2 R753Q (rs5743708) and TLR-4 D299G (rs4986790)	Low

Author	Country	Ethnicity	Type of allergy	Definition of Cases		Participants - Cases (sample size, age mean $\pm$ SD)		Participants - Controls (sample size, age mean $\pm$ SD)		Type of genetic study	Genes/SNPs of interest	Quality Score
Gaudieri, 2012 (15)	Australia	Caucasian	Food allergy and other allergy	History of reaction/doctor-diagnosis + SPT		35 allergic infants (cohort 1) + 30 children with FA (cohort 2), followed from birth to age 5 years		35 non-allergic infants, followed from birth to age 5 years		Candidate gene studies (no replication cohort)	tagSNP rs12979860 upstream of IL28B. 4 additional ones in LD (rs8403219, rs28416813, rs8103142 and rs4803217). Another tagging SNP rs8099917 10 kb upstream of IL28B	Moderate
Gawronska-Szklarz, 2001 (16)	Poland	White	Food allergy and other allergy	OFC + SPT + sIgE		136 children (61 with FA and other atopy, 75 with FA only), range 1.5 to 17 years		123 healthy children, range 2 to 17 years		Candidate gene studies (no replication cohort)	N-acetyltransferase 2 (NAT2) NAT2*4 allele, NAT2*5, NAT2*6, and NAT2*7	Low
Hand, 2004 (17) ⁺	UK	Majority Caucasian, some mixed race	Nut allergy	History of reaction + SPT		84 unrelated patients ranging from 3-56 years		1798 HLA typed random blood donors served as a population frequency control. Atopic control group of 82 random		Candidate gene studies (no replication cohort)	Polymorphisms within the HLA-A, B, DRB1, DQB1 loci	Low

Author	Country	Ethnicity	Type of allergy	Definition of Cases		Participants - Cases (sample size, age mean $\pm$ SD)		Participants - Controls (sample size, age mean $\pm$ SD)		Type of genetic study	Genes/SNPs of interest	Quality Score
								subjects with age range 16–61 years				
Hirota, 2017 (18)	Japan	Japanese	Food allergy	OFC or history of reaction	OFC or history of reaction	593 FA cases, 5.2 $\pm$ 3.7 years	279 cases, 5.8 $\pm$ 3.3 years	985 controls, 50.0 $\pm$ 9.2 years	886 controls, 50.6 $\pm$ 12.9 years	Candidate gene studies (with replication cohort)	19 and 7 susceptibility variants previously reported in GWAS for AD and EoE, respectively. FLG, C11orf30/LRRC32, TMEM232/SLC25A46, TNFRSF6B/ZGPAT, OVOL1, ACTL9,KIF3A/IL13, IL1RL1/IL18R1/IL18RAP, GLB1, CCDC80, GPSM3 (MHC region), CARD11, ZNF365, OR10A3/NLRP10, CYP24A1/PFDN4, IL2/IL21, PRR5L, CLEC16A/DEXT, ZNF652, TSLP/WDR36, CAPN14, XKR6, LOC283710/KLF13, C11orf30, STAT6, ANKRD27. Additional, 6 FLG null variants, c.3321delA, p.Q1701*, p.S2554*, p.S2889*,	Low

Author	Country	Ethnicity	Type of allergy	Definition of Cases		Participants - Cases (sample size, age mean $\pm$ SD)		Participants - Controls (sample size, age mean $\pm$ SD)		Type of genetic study	Genes/SNPs of interest	Quality Score
											p.S3296*, and p.K4022*,	
Hitomi, 2009 (19)	Japan	Japanese	Food-induced anaphylaxis, FA, AIA	OFC or History of reaction + sIgE		320 pediatric patients, 4.2 $\pm$ 3.3 years		254 children, 9.0 $\pm$ 1.7 years		Candidate gene studies (no replication cohort)	15 Tag SNPs of the exons and introns of NLRP3 with a minor allele frequency of greater than 10% in the HapMap Japanese data set rs2027432 rs12079994 rs4925648 rs4925650 rs12048215 rs10754555 rs3806265 rs10925019 rs4925654 rs4612666 rs10925026 rs12565738 rs4378247 rs10754558 rs10733112	Low
Hong, 2015 (20)	USA	European and non-European	Food Allergy, including peanut, egg and milk allergy	History of reaction + SPT/sIgE	History of reaction + SPT/sIgE	671 European food allergic cases, 155 non-European food allergic children.	62 PA European cases, 24 PA non-European cases, ranging from 0-21	144 non-allergic non-sensitized normal controls and 1,382 European controls of	69 European controls, 58 non-European controls, ranging from 0-21 years	GWAS	Genome-wide	High

Author	Country	Ethnicity	Type of allergy	Definition of Cases		Participants - Cases (sample size, age mean $\pm$ SD)		Participants - Controls (sample size, age mean $\pm$ SD)		Type of genetic study	Genes/SNPs of interest	Quality Score
						Children between 0-21 years old, parents information not available.	years	uncertain phenotypes (234 children and 1,148 parents). Children between 0-21 years old, parents information not available.				
Howell, 1998 (21)	UK	Cases all Caucasians	Peanut allergy	History of reaction + SPT		Study group: 34 nuclear families each containing one peanut allergic proband, three nuclear families each containing two peanut allergic siblings - 161 individuals: contained 50 peanut		293 bone marrow and cadaveric renal donors, age not provided		Candidate gene studies (no replication cohort)	HLA class II DRB1, DQB1 and DPB1	Low

Author	Country	Ethnicity	Type of allergy	Definition of Cases		Participants - Cases (sample size, age mean $\pm$ SD)		Participants - Controls (sample size, age mean $\pm$ SD)		Type of genetic study	Genes/SNPs of interest	Quality Score
						allergic individuals mean age 5 years, 34 non-peanut allergic siblings (of whom 12 were non-atopic and 22 atopic) plus non-peanut allergic parents						
Li, 2015 (22)	USA	European and African American	Food allergy	History of reaction + SPT/sIgE	History of reaction + SPT/sIgE	357 cases, 5.6 $\pm$ 4.4 years	167 cases, 5.4 $\pm$ 3.9 years	3980 controls, 10.2 $\pm$ 5.4 years	1573 controls, 12.6 $\pm$ 3.8 years	GWAS	Genome-wide	Moderate
Madore, 2013 (23)	Canada	Self-reported Caucasian	Peanut allergy	History of reaction + SPT/sIgE or SPT + sIgE or OFC		590 children. Post-QC: 311 children, 11 $\pm$ 4 years		332 children. Post-QC: 226 subjects, 4 $\pm$ 4 years		Candidate gene studies (no replication cohort)	HLA DQB1	Low

Author	Country	Ethnicity	Type of allergy	Definition of Cases		Participants - Cases (sample size, age mean $\pm$ SD)		Participants - Controls (sample size, age mean $\pm$ SD)		Type of genetic study	Genes/SNPs of interest	Quality Score
Marenholz, 2017 (24)	Germany, USA	European	Food allergy	OFC or History of reaction + sIgE	History of reaction + SPT/sIgE or OFC	523 children (n=497 after QC) Mean food allergy diagnosis 2.1 years	Replication 1: 380 German cases, 2.8 years mean food allergy diagnosis (n=379 after QC) Replication 2: 671 FA children, age not provided	2682 population-based, age not provided (N=2387 after QC)	Replication 1: 986 controls (n=984 after QC) Replication 2: 1526 controls Age not provided	GWAS	Genome-wide	High
Martino, 2017 (25)	Australia	European, Asian, mixed	Peanut allergy	OFC or recent reaction	OFC or recent reaction	73 infants, 12.8 $\pm$ 0.80 months	117 peanut allergic cases from various studies, age not provided	148 infants, 12.6 $\pm$ 0.67 months	380 non-allergic controls from HealthNuts and the Barwon Infant Study (BIS), age not provided	GWAS	Genome-wide	High
Pawlik, 2004 (26)	Poland	Caucasians and came from the Pomeranian region of Poland	Atopic disease including food allergy	OFC + SPT + sIgE		217 children (77 with food allergy) ranging from 1.5–17 years		124 healthy subjects ranging from 5–17 years		Candidate gene studies (no replication cohort)	FcyRIIa	Low

Author	Country	Ethnicity	Type of allergy	Definition of Cases		Participants - Cases (sample size, age mean $\pm$ SD)		Participants - Controls (sample size, age mean $\pm$ SD)		Type of genetic study	Genes/SNPs of interest	Quality Score
Savilahti, 2010 (27)	Finland	Not mentioned	Cow's milk allergy	OFC + SPT/sIgE		87 patients with CMA (67 IgE-mediated mean age 8.6 years, range 8.0-9.1 years and 20 non-IgE mediated mean 8.5 years, range 8-9 years		76 control subjects ranging from 8.1-9.3 years (mean 8.6 years)		Candidate gene studies (no replication cohort)	Panel of HLA class II haplotypes, PTPN22 R620W allele (rs2476601) and 5 filaggrin null mutations (del22824, 501-C/T, R2447X, S3247, 3702delG)	Moderate
Shreffler, 2006 (28)	USA	69 White, 4 Asian	Peanut allergy	History of reaction + sIgE		73 probands, mean age 6.5 years		75 siblings, mean age 8 years		Candidate gene studies (no replication cohort)	HLA DR and DQ: 10 individual DQB1 alleles, 65 allele groups DR	Moderate
Tamura, 2003 (29)	Japan	Japanese	Food-related anaphylaxis	History of reaction + sIgE		102 children with a major allergic disease including atopic dermatitis, bronchial asthma, and/or food-related anaphylaxis. 71 children had AD, 47		66 control subjects, age not provided		Candidate gene studies (no replication cohort)	STAT6: G2964A variant	Low

Author	Country	Ethnicity	Type of allergy	Definition of Cases		Participants - Cases (sample size, age mean $\pm$ SD)		Participants - Controls (sample size, age mean $\pm$ SD)		Type of genetic study	Genes/SNPs of interest	Quality Score
						had BA, and 14 had FA, age not provided						
Tan, 2012 (30)	Australia	Caucasian	Food allergy	OFC or SPT/sIgE or History of reaction		321 one-year-old infants		126 one-year-old infants		Candidate gene studies (no replication cohort)	FLG: R501X, 2282del4, R2447X, S3247X and 3702delG	Low
Venkataraman, 2014 (31)	UK	Not mentioned	Food allergy	History of reaction +/- SPT		1374 children aged 1 year 1231 children aged 2 years 1218 children aged 4 years 1373 children aged 10 years 1313 children aged 18 years 1150 18-year-old children genotyped				Candidate gene studies (no replication cohort)	FLG: R501X, 2282del4, S3247X, 3702delG and R2447X	Moderate

Author	Country	Ethnicity	Type of allergy	Definition of Cases		Participants - Cases (sample size, age mean $\pm$ SD)		Participants - Controls (sample size, age mean $\pm$ SD)		Type of genetic study	Genes/SNPs of interest	Quality Score
Woo, 2003 (32) ⁺	USA	White and mixed	Food allergy	OFC or History of reaction + SPT/sIgE		77 patients 5.2 $\pm$ 5.3 years (range 0.8-33.9 years)		61 non-atopic, non-asthmatic control adults 29.9 $\pm$ 7.4 years (range 20-51 years)		Candidate gene studies (no replication cohort)	CD14: -159 C $\rightarrow$ T	Low
Brough, 2014 (33)	UK	FLG genotype: only white, other analysis non-white inclusive	Peanut allergy	OFC or History of reaction + SPT/sIgE		20 children with peanut allergy at age 8, 11 years or both		577 children without peanut allergy at age 8, 11 years or both		Candidate gene studies (no replication cohort)	FLG R501X, S3247X, R2447X. 2282del4, 3673delC and 3702delG	Low
Koplin, 2016 (34)	Australia	Caucasian and Asian	Food Allergy	OFC + SPT/sIgE		338 food-allergic at age 1 55 with persistent egg allergy at age 2		269 non-allergic at age 1 50 with resolved egg allergy at age 2		Candidate gene studies (no replication cohort)	GC: rs7041 and rs4588	Moderate

⁺ Studies carried out in participants across ages including children

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