Meta-analysis of genome-wide association studies of food allergy and IgE-sensitization

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Meta-analysis of genome-wide association studies of food allergy and IgE-sensitization

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Meta-analysis of genome-wide association studies of food allergy and IgE-sensitization

Maier et al, J Allergy Clin Immunol (2026)

Study population

Discovery

Adults (N=229,426, 13 cohorts)

Children (N=14,234, 16 cohorts)

Replication

Adults: N=368,203
Children: N=944

Validation

Children: N=5,865

Multi-Phenotype GWAS Meta-analysis

- Self-reported food allergy
- Doctors-diagnosed food allergy
- Food-specific sensitization
- Doctors-diagnosis + sensitization

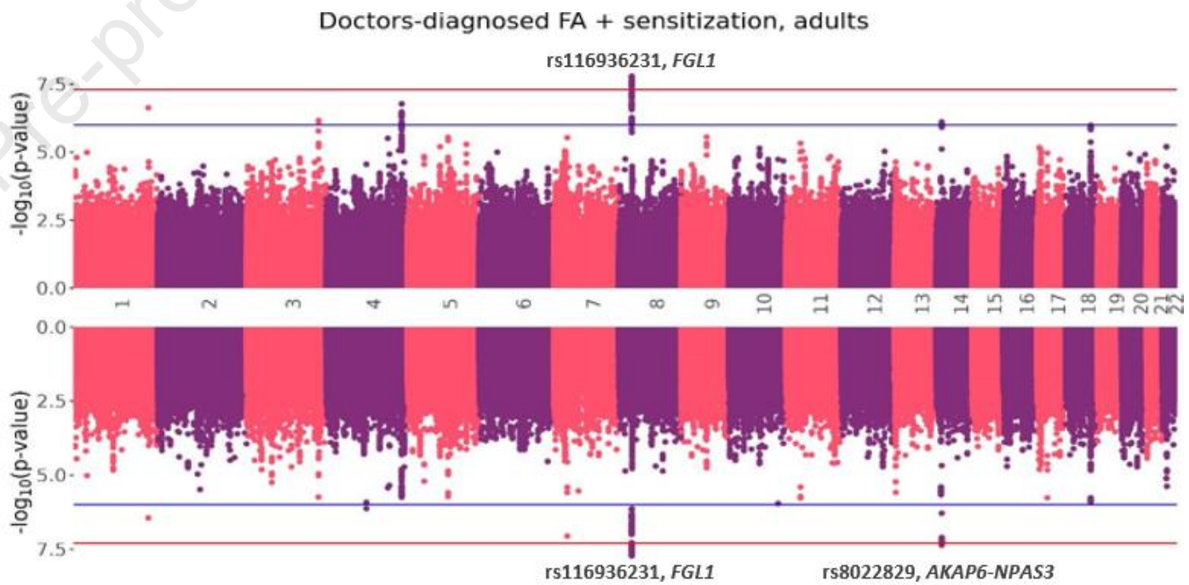
+ Sensitivity analysis
additional adjustment for hay fever

+ Validation
Oral food challenge confirmation

Results

Discovery phase

- 37 suggestive loci ($p<10^{-6}$)
- Two genome-wide significant loci in adults



No successful replication or validation in oral food challenge phenotype

Take home messages

1. Food allergy is not a genetically uniform condition
2. Distinct genetic architecture across age groups
3. Large genetic overlap with other allergy phenotypes
4. Need for unified assessment and definition

GWAS = genome-wide association study; FA = food allergy

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Abstract

Background: Food allergies (FA) arise from a complex interplay between an individual's genetic predisposition and environmental factors and their prevalence is increasing. Genome-wide association studies (GWAS) to date have been hindered by small sample sizes and varying FA definitions.

Objective: Identify novel food allergy risk loci by conducting a GWAS meta-analysis in children and adults using a multi-phenotype approach to ensure the trade-off between sufficient sample size and valid FA definitions.

Methods: Analyses were conducted separately in children and adults based on the following FA phenotypes: self-report, doctors-diagnosis, food-specific sensitization, and doctors-diagnosis plus food-specific sensitization. GWAS from up to 16 cohorts of European ancestry including 229,426 adults and 14,234 children were meta-analyzed. Models were adjusted for sex, age, principal components, and if applicable, further study-specific confounders. Sensitivity models were additionally adjusted for hay fever. Replication was conducted in additional external cohorts and a validation in oral food challenge-defined FA cases.

Results: 37 SNPs met suggestive significance (p-value < $1x10^{-6}$), with two reaching genome-wide significance: rs116936231 (*FGL1*) in adult doctors-diagnosed FA plus food-specific sensitization phenotype (stable after additional hay fever adjustment) and rs8022829 (*AKAP6-NPAS3*) which was significant only in the hay fever-adjusted model in adults. However, neither variant was validated. Further, we identified three SNPs previously reported for FA and atopic diseases.

Conclusion: This study identified 37 SNPs suggestively associated with FA and demonstrated genetic differences across phenotypes. It highlights the need for a unified FA definition and sheds light on its shared genetic architecture with allergies.

Key message (2-3 short bullet points max):

- This GWAS meta-analyses on FA comprising 229,426 adults and 14,234 children identified 37 suggestive SNPs with two SNPs reaching genome-wide significance.
- Although these associations were not replicated after multiple testing adjustments, these findings highlight potential genetic associations and their overlap with other allergic phenotypes.
- The study further revealed distinct differences across FA definitions, underscoring that FA is a genetically heterogeneous definition and indicates that doctor-diagnosed food allergy provides the most reliable phenotype for future analyses

Capsule summary (33/35 words max): This GWAS meta-analysis identified 37 SNPs suggestively associated with FA, revealing genetic differences across age groups and FA definitions, alongside overlaps with other atopic diseases, providing valuable insights into genetic susceptibility to FA.

Key words (7/10 max): genome-wide association study, food allergy, meta-analysis, specific IgE, hay fever, sensitization, epidemiology

Abbreviations: FA (food allergy), GWAS (genome-wide association studies), SNP (single nucleotide polymorphism), OFC (oral food challenge), IgE (immunoglobulin E), sIgE (specific immunoglobulin E), SPT (skin prick test), PFAS (pollen-food allergy syndrome), HWE (Hardy-Weinberg Equilibrium), MAF (minor allele frequency), LD (linkage disequilibrium), COJO (conditional and joint analysis), IBD (identical by descent), LDSC (linkage disequilibrium score regression), eQTL (expression quantitative trait loci), MAGMA (Multi-marker Analysis of GenoMic Annotation), FDR (false discovery rate), CADD (combined Annotation Dependent Depletion), LoF (loss of function), pLI (probability of being loss-of-function intolerant), EMAC (estimated minor

allele count), CysLT (cysteinyl leukotriene), DPEP1 (disproportionating enzyme 1), PRS (polygenic risk score)

Introduction

Food allergy (FA) is a complex disease defined as an adverse response of the immune system to innocuous food proteins mediated by specific Immunoglobulin E (sIgE) (1). FA prevalence verified by the diagnostic gold standard, oral food challenge (OFC), is 4.2% in white children (2) and 3.7% in white adults (3) whereas the prevalence of self-reported FA is up to six times higher (4). Differences in the manifestation of the allergic reactions complicate an accurate diagnosis (5). Since OFCs are resource-intensive and carry the risk of anaphylaxis, challenge-confirmed FA data are rare in population-based studies. Alternatively, the presence of food-specific sensitization assessed by sIgE measurements or skin prick tests (SPT) together with a history of FA specific symptoms may be used for diagnosis (6).

FA susceptibility is strongly influenced by genetics, with twin-study heritability estimates ranging from ~51% to 82% (10). Recent genome-wide association studies (GWAS) on FA mainly revealed genetic associations implicating genes involved in skin barrier function and immune regulation with 18 risk loci associated with FA identified to date (11-17). These variants account for a limited proportion of heritability (11), suggesting further risk variants remain to be identified. Sufficiently powered, large-scale GWAS meta-analyses are currently lacking (8, 10), but would allow detection of variants with smaller effect sizes and/or allele frequencies. Furthermore, most genetic studies of FA have focused on pediatric patients which have been characterized by comprehensive clinical phenotyping and are often targeted to specific allergens (12, 15, 17). The etiology of food allergies exhibits notable differences between children and adults as mechanisms of sensitization, allergens and clinical presentation vary by age (18). In adults, pollen sensitization is highly prevalent and contributes to secondary FA due to allergen cross-reactivity (6, 19, 20).

Therefore, we performed a meta-analysis of GWAS on FA phenotypes stratified for child and adult cohorts using the largest assembly of studies to date comprising 14,234 children and 229,426 adults of European ancestry. Four FA phenotypes were defined with increasing diagnostic certainty to maximize collaborative sample size while balancing the risk of misclassification. Identified candidate SNPs were validated in subjects with OFC-proven FA. Sensitivity analyses with additional adjustment for hay fever were performed to differentiate between SNP effects on primary and secondary FA. Primary FA results from a direct immune response to a specific food allergen, while secondary FA occurs due to cross-sensitization with aeroallergens triggering reactions to certain foods with similar protein structures. For example, apple allergy often reflects IgE-mediated cross-reactivity between homologous proteins in birch pollen and apple, rather than

primary sensitization to apple itself. This reaction is then defined as pollen-food allergy syndrome (PFAS) (21).

Methods

The overview of the study design can be found in Figure 1. Study protocols were approved by the local ethics committees of the respective cohorts (Supplementary Note).

Phenotype definition

Cases were defined as those who ever (a) self-reported any FA (compared to those never reporting any FA), (b) self-reported a doctors-diagnosed FA (compared to those never reporting a doctors-diagnosed FA), (c) showed positive food-specific sensitization measured via skin prick test or sIgEs (≥0.35kU/L) (compared to those without food-specific sensitization), (d) reported a doctors-diagnosed (or self-reported) FA and showed positive food-specific sensitization (compared to those who never reported any FA and do not have food-specific sensitization). Details on cohort-specific definitions can be found in Supplementary Note and sample sizes per phenotype in Supplementary Table E1.

Association and quality control analyses

GWAS were performed in each cohort by single variant tests using logistic regressions under an additive model, including only genetic variants at autosomal chromosomes. Details on genotyping, genotype imputation, quality control, and software tools are provided in the Supplementary Note. Main association models were adjusted for sex, age, genetic principal components, with the number of components varying by study, and, if applicable, study-specific potential confounders. The exact numbers of principal components and details of confounders are shown in Supplementary Table E2. To differentiate between primary and secondary FA, a sensitivity analysis was conducted additionally adjusting for hay fever. However, it has to be considered that the adjustment for hay fever may reduce confounding but at the same time obscure shared genetic effects.

Standardized quality control of cohort summary statistics included checks for completeness, formatting, duplicates, monomorphic SNPs, nonsense values, Hardy-Weinberg violations (HWE $P<1e^{-6}$) (22), low imputation quality variants (R2≤0.5, INFO score≤0.4) (23), low estimated minor allele count (EMAC=2*N*minor allele frequency (MAF)*imputation quality score≤50) (24), and MAF≤1%. Further steps addressed strand flip issues, allele miscoding, and ancestry mismatches, with Manhattan plots and QQ-plots generated for visual validation.

Discovery meta-analyses

Cohort-specific GWAS results were meta-analyzed using an inverse-variance weighted fixed effect model with genomic control using GWAMA (25). Meta-analyses were conducted by FA phenotype and age group (children (<18 years) and adults). Heterogeneity between studies was assessed by using Cochran's Q statistic and I^2. Variants with Cochran's heterogeneity p-value≤0.05 and present in less than three studies were excluded.

Identification of risk variants and lead SNPs

FUMA v1.5.2 (26) was used to identify lead SNPs in candidate regions. SNPs meeting suggestive significance (p-value<1×10^{-6}) were first clumped using the 1000 Genome Phase 3 reference of European ancestry at $r^2<0.6$ to identify independent significant SNPs. A second clumping at $r^2<0.1$ was then performed to pinpoint the lead SNPs.

Novel/known assignment

Known loci were defined as SNPs in linkage disequilibrium (LD) (pairwise $r^2\geq0.1$) with previously published variants associated with FA or other allergic diseases (Table E3). To differentiate between novel and known loci, these variants were also tested for the association with all definitions of FA in the discovery set with a nominal p-value threshold of $p<0.05$.

Replication

Identified lead variants from the discovery were taken forward for replication. External replication using additional cohorts was performed in a) self-reported FA in adults, b) doctors-diagnosed FA in adults, and c) food-specific sensitization in children. Additionally, a validation study was carried out in an independent sample of children with OFC-confirmed FA (Table E2, E4) and applied a Bonferroni-corrected alpha threshold.

Conditional analysis

Independent association signals were identified among the significant genetic variants through conditional analyses, performed using GCTA-COJO and summary statistics from the meta-analysis and LD correlations between SNPs. A LD correlation matrix was estimated based on a subgroup of the Lifelines cohort (27) that was not used for meta-analysis. We excluded one individual from each pair with a genetic relatedness (IBD) above 0.1875, retaining 9,027 unrelated individuals of the Lifelines subcohort. LD correlations were disregarded for SNPs over 20Mb apart or on different chromosomes to avoid sample overlap in subsequent analyses. Suggestive significance threshold (p-value<1×10^{-6}) was applied for the SNP selection.

Linkage disequilibrium score regression for heritability estimation

We used the linkage disequilibrium score regression (LDSC) method (software LDSC v1.0.1) (28) to determine the SNP-based heritability (h^2_{SNP}) for each FA phenotype. The 95% confidence intervals (CI) were calculated using the Wald method. This analysis was conducted using summary statistics from the discovery meta-analyses. Heritability calculations were adjusted to a liability scale, considering a population prevalence of 0.1 (29), with sample prevalence calculated for each FA phenotype separately. LDSC estimates the genetic heritability contributed by common variants genome-wide, incorporating both significant and sub-threshold SNPs.

Genetic correlations were assessed using all available 1,639 traits on CTG-VL (30) (accessed October 4th, 2024). We identified nominally significant genetic correlations ($p<0.05$) and applied a Bonferroni-corrected alpha threshold of 0.05/1639 (p-value$<3.05\times10^{-5}$) to identify significant correlations. Genetic correlation analysis was limited to phenotypes with positive SNP-based heritability (h^2_{SNP}), total h^2>total h^2 SE and z-score (calculated as total h^2/total h^2 SE) > 1.5. Genetic correlation values were restricted to those ranging between -1 and 1.

Functional annotations and gene mapping

MAGMA (MAGMA v1.08) enrichment analysis using RNA sequencing data from GTEx v.8 (31) was conducted for 54 tissue types. Further, MAGMA was used to perform gene-based tests and gene-set analysis.

All lead SNPs eligible for replication and variants in LD ($r^2\geq0.6$) with them were annotated using FUMA v1.5.2 (26). ANNOVAR v2017-07-17 was used to obtain the functional consequences of SNPs on the respective genes. Three complementary gene prioritization methods were used: positional mapping (associating variants with nearby protein-coding genes within ±10kb using ANNOVAR annotation), expression quantitative trait loci (eQTL) mapping (linking SNPs to tissue-specific eQTLs with FDR<0.05 within ±1Mb as cis-eQTLs), and chromatin interaction mapping (identifying long-range interactions by mapping variants to genes with promoter regions overlapping significant chromatin interactions, defined as 250bp upstream and 500bp downstream of the transcription start site, with an FDR threshold of 1×10^{-6}).

Results

GWAS meta-analysis of discovery population

GWAS results from 16 cohorts of European ancestry totaling up to 229,426 adults and 14,234 children were meta-analyzed separately by age group and phenotype: self-reported ($cases_{adults}$=5,048, $cases_{children}$=2,203), doctors-diagnosed ($cases_{adults}$=1,315, $cases_{children}$=1,090), food-specific sensitization ($cases_{adults}$=889, $cases_{children}$=1,891), and reported FA plus food-specific sensitization ($cases_{adults}$=279, $cases_{children}$=558). Numbers per study are depicted in Table E1. There was no evidence for population stratification with genomic inflation factors λ ranging from 0.93 to 1.00 (Table E5, Figure E1). Figure 2 shows effect sizes of the lead SNPs for each phenotype and age group. Stronger effects were observed for more stringent phenotype definitions. The discovery meta-analyses on doctors-diagnosed FA plus food-specific sensitization in adults (N_{main}=4,322, $N_{hayfever}$=4,296) revealed two novel loci at genome-wide significance ($p<5\times10^{-8}$): rs116936231 near *FGL1* (main model: OR=4.76, $p=1.62x10^{-8}$; hay fever-adjusted: OR=5.03, $p=1.86x10^{-8}$) and rs8022829 near *AKAP6-NPAS3* (OR=2.23, $p=4.31x10^{-8}$), with the latter being significant only in the hay fever-adjusted model (Table 1; Figure 3). The forest plot showed consistent direction and magnitude of the effect across studies (Figure E4). Moreover, a further 35 signals yielded suggestive significance ($p<1x10^{-6}$) (Table E6, Figure E2), of which two were removed from the lead SNPs eligible for replication due to significant between study heterogeneity (Cochran's heterogeneity p-value<0.05). The conditional analysis revealed no additional independent associations (Figure E5). Using a more stringent phenotype definition, we identified stronger genetic signals.

Overlap of lead SNPs with other allergic traits

Heatmaps were used to visually compare the effects of previously identified allergy associated SNPs related to FA (p-value<0.05) across the FA meta-analyses (Figure E6). In total, 229 of 472 SNPs showed association with more than one FA phenotype, including variants in the *FLG* and *HLA* loci (Table E28). Three of the lead SNPs have been previously reported to be associated with allergy phenotypes, based on LD calculation (Table 2). The variant rs2033784 near *SMAD3* is in strong LD (r^2=0.7) with variants previously associated with asthma (32), atopic disease (33), allergic rhinitis (34), and age of allergy onset (35). Another variant in LD with rs66609926 (r^2=0.12) near *AC010733.4* has been associated with atopic dermatitis (36). Additionally, rs998706 within a ±1Mb window with our lead variant rs6007514 has been associated with peanut allergy (37). Since rs6007514 is not in the used 1000G reference panel, it was not possible to calculate LD,

but the physical proximity and assignment to the same gene, *FAM118A*, suggest these may represent the same signal.

LD score regression revealed nominally significant genetic correlations for food-specific sensitization with atopic diseases, allergic rhinitis, and eosinophil count (p-value<0.01), suggesting a shared genetic basis between FA allergic conditions (Table E7-E8).

Furthermore, we compared previously identified FA related variants with our findings. Eight SNPs in children, and six SNPs in adults showed nominal significance (p-value<0.05) in this study, with most of these associations being observed with the more stringent phenotypes. Some of these SNPs are located at the *HLA* region. We also found consistent magnitudes and directions of effect, except for results from one study in a Japanese cohort (Table E9-E10).

Through replication of previous findings and genetic correlation analyses, we confirmed that food allergy shares a genetic basis with other allergic diseases.

Comparison of association across main and hay fever-adjusted models

Odds ratios and 95% confidence intervals of the 37 lead variants were compared across the main and hay fever-adjusted models. Strong and statistically significant Pearson correlations (0.96-1.0), along with directional consistency of genetic effects between both models were found for all variants across phenotypes in children and adults (Figure E7).

Comparison of associations between pediatric and adult cohorts

Effect sizes and directions differed markedly between pediatric and adult cohorts, and none of the correlation coefficients were significant (Figure E8), suggesting a marked difference in the genetic architecture of FA in pediatric and adult cohorts. Consistent effect directions were observed for only 50% of lead SNPs in the food-specific sensitization phenotype. For self-reported and doctors-diagnosed FA, 62% and 65% of the lead SNPs, respectively, showed the same direction of effect. In contrast, for self-reported FA plus food-specific sensitization, 75% of effects were consistent. In summary, children and adults were analyzed in separate groups due to established clinical differences, and any contrasts observed reflect differences across these age-defined study populations rather than direct comparisons of age-of-onset of the disease.

Replication

The 37 lead SNPs identified in the discovery phase were tested for replication in 7 external cohorts using available phenotypes. These included self-reported FA in adults using the publicly available

UK Biobank data (38) (N_{total}= 361,141), doctors-diagnosed FA in adults using the EXCEED cohort (N_{total}=7,062) and food-specific sensitization in children from the GENEVA and CLARA/CLAUS cohorts (N_{total}=944) (Table E4). An additional validation study was conducted in a dataset comprising pediatric FA cases defined by OFC in children (GENEVA, GOFA, MAAS, HealthNuts cohorts; N_{total}=5,865). The variant rs11643761 which yielded suggestive significance in the food-specific sensitization phenotype in children demonstrated consistent direction of effects in the replication for the same phenotype as well as in the validation study with OFC (Table 3). The direction of effects from the OFC validation study was consistent for 58.8% of the variants and a comparison of effect direction in adults between discovery and replication of doctors-diagnosed FA showed 68.8% consistent effect directions (Table 4). The variants rs73228469, rs138021736, and rs6230534, which reached suggestive significance in the discovery phase, showed the same direction of effects in the corresponding replication study but did not reach statistical significance. However, none of the candidate SNPs reached the Bonferroni-adjusted significance threshold in the replication phase (Table 3, Table 4). In this analysis, we were unable to replicate the initial genetic associations.

SNP-based heritability

In children, the SNP-based heritability (h^2_{SNP}) estimated using LDSC was 8.9% (95% CI: -5.6%; 23.5%) for self-reported FA adjusted for hay fever, and 30.6% (95% CI: -14.7%; 75.8%) for the combination of doctor-diagnosed FA and food-specific sensitization. Similarly, in adults, the h^2_{SNP} was 34.0% (95% CI: 1.9%; 66.0%) for food-specific sensitization and 37.6% (95% CI: 6.8%; 68.5%) for food-specific sensitization adjusted for hay fever. For the remaining phenotypes, the heritability estimates were either negative or the total h^2 was smaller than the standard error of the estimate (Table E11). For the more objectively defined phenotype based on sensitization, we estimated a substantial SNP-based heritability.

Functional annotation and biological interpretation

MAGMA identified thyroid to be the most enriched tissue among genes mapped for the doctors-diagnosed FA phenotype in adults (Figure E9). In children, brain, heart, and pituitary tissues were significantly enriched across phenotypes (Figure E9). Gene-sets of the prefrontal cortex were significant in the doctors-diagnosed FA phenotype in children with hay fever adjustment (Table E12). Gene-based tests did not show any significant results (Figure E10-E11).

Genes were mapped per age group, phenotype, and model based on position, eQTL and chromatin interaction (Table E13-E27). There was no overlap of genes across the phenotypes for

adults within the main and hay fever-adjusted models (Figure E12 C-D). In children, there were two overlapping genes in the hay fever-adjusted meta-analyses (Figure E12 B). Both genes, *EOGT* and *FAM19A1,* were mapped by chromatin interaction in the self-reported and doctors-diagnosed plus food-specific sensitization phenotype and are protein-coding genes located on chromosome 3. *FAM19A1* has a probability of being loss-of-function (LoF) intolerant (pLI) score of 0.86 which is close to the LoF intolerance threshold of 0.9 (39). Annotation of functional consequences of all variants in LD with the lead SNPs (r^2>0.6) demonstrated that these were mostly located in intronic and intergenic regions.

Discussion

In this GWAS meta-analysis of food allergy and food-specific sensitization, the genetic architecture of various FA phenotype definitions was explored in up to 14,234 children and 229,426 adults. Thirty-seven loci that were identified suggestively linked to at least one FA phenotype. Variants in two loci, located at *FGL1* and *AKAP6-NPAS3*, reached genome-wide significance in the doctors-diagnosed FA plus food-specific sensitization phenotype in adults. Stronger genetic effects were evident when applying more stringent disease definitions, with genome-wide significant hits identified only in the doctors-diagnosed FA plus food-specific sensitization phenotype despite the smaller sample size. This highlights that a stricter definition, incorporating objective measurements (such as sensitization), offers the most powerful yet tractable approach for future large-scale genetic discoveries in FA research. Studies of allergic diseases show that well-defined phenotypes, such as childhood-onset asthma or specific food allergies, can reveal strong genetic signals even in smaller cohorts, whereas broad, heterogeneous definitions might dilute associations despite larger sample sizes (40, 41). Heterogeneity of effects were observed between children and adult cohort. Moreover, we provide evidence for shared genetic susceptibility of FA with asthma, rhinitis, and atopic dermatitis.

One of the two genome-wide significant FA-SNP associations was located near *FGL1*, which is engaged in inflammatory immune responses (42). This gene encodes a member of the fibrinogen family and is involved in processes of the immune system by suppressing T-cell mediation (42). *FGL1*-knockout mice have been observed to develop spontaneous dermatitis and autoimmune diseases (42). One of the candidate genes at the second locus, *NPAS3* had been linked to asthma in populations of European and African ancestry (43) and both *AKAP6* and *NPAS3* have been reported to potentially play a role in metabolic syndrome (44). The results of this study also revealed genetic variants associated with FA that have been previously associated with other atopic diseases. Notably, variants at *SMAD3* have been associated with asthma, allergic rhinitis, atopic dermatitis, and age of allergy onset, reinforcing previous observations of shared genetic architecture across allergic conditions (32-36). *KCNIP4*, *CASP4* and *CASP5*, which were associated with doctors-diagnosis of FA plus food-specific sensitization, are also known to play roles in allergic airway inflammation and pathophysiology of asthma (45, 46). These genes further support the concept of shared genetic background among atopic diseases and their underlying immunological pathways, and they were all captured by analyses using the more stringent phenotypes. More precise phenotype definitions performed better overall. Including food-specific sensitization as an objective measurement may help to reduce the risk for misclassification in

studies of FA, as it may more reliably reflect heritability. This assumption is confirmed by the observed higher heritability for the food-specific sensitization phenotype. However, this does not apply to the validation study using cohorts with OFC-confirmed FA, where no significant associations were found. The different phenotype definitions used in this study yielded highly variable SNP-based heritability estimates. For the broader phenotypes, such as self-reported FA, we did not detect a significant heritable component (adults: h2=0.4% 95% CI: -4.7%; 5.6% and children: h2=2.4% 95% CI: -9.2%; 13.9%). In contrast, the more stringently defined phenotypes incorporating food-specific sensitization showed substantial SNP-based heritability (h2=34.0% 95% CI: 1.9%; 66.0%) in adults). This difference likely reflects heterogeneity and misclassification within the broader phenotype groups, which dilute genetic signal and reduce power to detect both heritability and significant genome wide associations. These findings suggest that such broad case definitions are not optimal for genetic studies, whereas more precise phenotyping yields clearer evidence of heritable contributions. A potential source of heterogeneity is that self-reported food allergy does not differentiate primary FA from secondary FA (PFAS). However, the observed heritability reflects the cumulative contribution of numerous small-effect SNPs rather than solely genome-wide significant loci, although LDSC heritability estimates are subject to considerable uncertainty due to large standard errors and should be interpreted with caution.

This distinction is crucial for genetic studies, as these conditions are clinically and genetically distinct (19). Besides that, another potential explanation is that a patient can be sensitized (having food allergen specific IgE) but have low gut permeability at the time of the OFC leading to a negative or tolerant outcome. In a recently published mouse model of FA, this was influenced by reduced local bio-availability of cysteinyl leukotrienes (CysLT) and presence of disproportionating enzyme 1 (DPEP1) activity (47, 48), suggesting that barrier/epithelial–mast cell crosstalk is a key determinant of clinical reactivity upon ingestion. Together, these data support the idea that OFC-positive cases represent a biologically more homogeneous, gut-centric endotype; loci detected in broader, diagnosis/sensitization-based GWAS may therefore show weaker or absent effects in OFC cohorts unless they influence these mucosal leukotriene/mast-cell pathways.

Our analysis also revealed distinct genetic architectures for FA in children and adult cohorts, characterized by age-specific associations and, for some loci, effects in opposing directions across age groups. Moreover, SNPs with the effect allele associated with higher FA risk were linked to a lower age of allergy onset. Age-related differences were further supported by the SNP-heritability estimates observed. Specifically, SNP-heritability was 30% for food-specific sensitization in adults, 9% for self-reported FA in children, and 30% in doctors-diagnosed FA plus

food-specific sensitization phenotype in children. While these results reflect the aggregate contribution of widespread common variants, the standard errors were larger for the childhood estimates compared to adults. Therefore, the precise magnitude of these heritability estimates should be interpreted with caution. Heritability could not be estimated for the remaining phenotypes, potentially due to limited sample size, or phenotype misclassification. These findings suggest significant genetic heterogeneity between childhood and adulthood FA, underscoring the need for age-stratified analyses in future genetic studies.

We also investigated variants previously reported to be associated with FA (10), of which 8 were nominally associated in children and 6 in adults in this study (p-value<0.05). Although no loci were significantly associated after multiple testing correction, these observations further support the hypothesis that a strict definition of FA might account for a larger proportion of FA variability (10). The nominally associated SNPs were mostly located in the *HLA* region, highlighting the critical role of immunological mechanisms in general FA. Our study also confirmed that FA shares genetic risk factors with other allergic diseases (32-36). Of 472 SNPs associated with allergic conditions, 229 loci were also associated with at least one FA phenotype (P<0.05), for example *FLG* (Table E28). Furthermore, genetic correlation analysis showed associations between FA and other allergic traits, emphasizing an underlying shared genetic risk profile, particularly the central role of IgE-mediated sensitization.

A major strength of this study lies in its scale, which reflects extensive efforts to uncover SNPs associated with FA. This is the largest genetic investigation of FA to date, uniquely integrating multiple phenotypes across multiple layers of evidence to explore associations in both pediatric and adult populations.

However, this study also has several limitations. Firstly, analyses were restricted to individuals of European ancestry. Second, despite the large sample size, phenotype misclassification and heterogeneity remained an issue. There is potential misclassification of FA, particularly when using questionnaire data and heterogeneity can exist between and within populations, including differences in the study design, age, as well as heterogeneity in FA itself. These challenges further highlight the need for a standardized questionnaire on FAs in population-based studies to improve phenotype accuracy and reliability and enable meaningful comparisons across cohorts. Moreover, this study demonstrates the challenge in analyzing general FA phenotypes and identifying general risk factors due to the diverse manifestations of FA. Further, we also lack the age of disease onset for all participants, which prevented us from performing stratified analyses to investigate the potentially distinct genetic architectures of childhood-onset versus adult-onset FA. Addressing

misclassification and heterogeneity will be essential for advancing the understanding of genetic risk factors for FA. Another limitation of this study is the absence of HLA-specific imputation, which prevented high-resolution analysis of genetic variation in this region. Moreover, pooling different food allergy phenotypes without such imputation may have diluted locus-specific signals making it difficult to detect associations in this highly relevant region. Finally, a limitation of this study is the increased multiple testing burden arising from performing multiple meta-analyses across different phenotypes and sensitivity analyses.

This GWAS meta-analysis, the largest conducted to date on FA, identified 37 SNPs with suggestive associations, highlighting genetic distinctions between FA in childhood and adulthood, across phenotypes and age groups as well as shared genetic factors with other atopic conditions These findings provide important insights in the genetic basis of FA and provide a foundation for future research. Further, this study highlights the challenge of balancing accuracy of phenotype definition with sample size. It underscores the importance of improving data collection and harmonization of assessment methods to facilitate large collaborative studies. While broader phenotype definitions may enhance power to identify genetic associations with atopic diseases, the inherent heterogeneity of FA necessitates collaborative efforts to refine research approaches allowing also to investigate specific food allergens. In addition, creating a polygenic risk score (PRS) to sum up the many small effects of many variants into a single risk metric may provide additional insights.

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Figure 1: Overview of GWAS meta-analysis and replication study design.

Figure 2: Heatmap of effect estimates from GWAS meta-analyses by phenotype and age group for 37 lead SNPs. Lead SNPs are indicated on the y-axis and the results per phenotype and model are displayed on the x-axis. Asterix indicate the trait where the significance threshold ($p < 1 \times 10^{-6}$) was passed in the discovery. Genome-wide significant SNPs are outlined with a box including the mapped gene.

Figure 3: QQ plots for doctors-diagnosed food allergy plus food-specific sensitization in adults based on results from **A** main model and **B** hay fever adjusted model. **C** Miami plots of meta-analyses for doctors-diagnosed FA plus food-specific sensitization in adults. Mirrored plots display the baseline model of the respective phenotype on the top and the hay fever-adjusted model on the bottom. Blue line indicates suggestive significance ($p < 1 \times 10^{-6}$) and red line genome-wide significance ($p < 5 \times 10^{-8}$).

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Contributions:

Designed and coordinated the study: L.M., Y.S., E.T.G.K., J.M.V., E.T., G.H.K., M.S.

Performed the meta-analysis: L.M.

Performed the bioinformatic analysis: L.M., Y.S.

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Table 1: Novel suggestive and genome-wide significant lead SNPs from discovery meta-analyses.

Variant	Chr:position	Gene	Trait	Model	Age group	EA/NEA (EAF)	OR (CI)	P	I2 (%)	Het Q P	N (studies)
rs116936231	8:17753408	FGL1	doctors-diagnosed FA + sensitization	main, hay fever	adults	T/C (0.02)	4.76 (2.77 - 8.18)	1.62E-08	0	0.757	3047 (3)
rs8022829	14:33397346	AKAP6, NPAS3	doctors-diagnosed FA + sensitization	main, hay fever	adults	A/G (0.09)	2.23 (1.68 - 2.98)	4.31E-08	0	0.628	4026 (5)
rs6833463	4:21244175	KCNIP4	doctors-diagnosed FA + sensitization	main	children	A/G (0.24)	1.5 (1.3 - 1.74)	5.05E-08	0	0.819	5571 (7)
rs11761070	7:24587280	MPP6, RNU6-1103P	doctors-diagnosed FA + sensitization	hay fever	adults	C/A (0.07)	2.89 (1.96 - 4.26)	8.70E-08	0	0.764	3031 (3)
rs74531285	2:197132359	HECW2	doctors-diagnosed FA	main	children	T/C (0.02)	2.42 (1.75 - 3.36)	1.28E-07	15	0.321	8497 (5)
rs78609709	2:53770433	GPR75-ASB3	doctors-diagnosed FA + sensitization	hay fever	children	C/A (0.04)	2.4 (1.73 - 3.32)	1.40E-07	26	0.236	5188 (6)
rs117319649	10:47668777	ANTXRL	sensitization	main, hay fever	adults	T/G (0.04)	2.52 (1.79 - 3.57)	1.58E-07	0	0.780	3247 (3)
rs72705776	4:180911393	RP11-774G5.1, RP11-751A18.1	doctors-diagnosed FA + sensitization	main	adults	T/C (0.09)	2.13 (1.61 - 2.83)	1.66E-07	35	0.190	4050 (5)
rs1022311	2:180555884	ZNF385B	doctors-diagnosed FA	main, hay fever	children	T/C (0.1)	1.48 (1.28 - 1.72)	1.80E-07	7	0.374	10544 (8)
rs16849773	1:202204213	LGR6	sensitization	main	adults	A/G (0.02)	2.4 (1.72 - 3.34)	2.46E-07	31	0.237	3056 (3)
rs55681581	5:126981185	PRRC1, CTXN3	self-reported FA	main	children	T/C (0.15)	1.37 (1.22 - 1.55)	2.74E-07	0	0.526	12514 (9)
rs11645276	16:53092980	CHD9	doctors-diagnosed FA + sensitization	main	children	C/T (0.4)	0.68 (0.59 - 0.79)	3.07E-07	0	0.844	5571 (7)
rs62248296	3:68324177	FAM19A1	self-reported FA	hay fever	children	G/A (0.19)	1.44 (1.25 - 1.66)	3.43E-07	32	0.194	6651 (6)
rs74991536	1:231163221	FAM89A	doctors-diagnosed FA	main, hay fever	children	C/T (0.98)	0.44 (0.32 - 0.61)	3.49E-07	35	0.174	9405 (6)
rs76119799	2:212415241	ERBB4	self-reported FA	main, hay fever	children	T/G (0.05)	0.52 (0.41 - 0.67)	3.92E-07	20	0.279	8627 (6)
rs73174808	3:177288324	LINC00578	self-reported FA	main	children	C/A (0.06)	1.59 (1.33 - 1.91)	4.02E-07	0	0.837	12883 (9)
rs2055684	3:69108316	UBA3	doctors-diagnosed FA + sensitization	main, hay fever	children	A/T (0.47)	0.7 (0.61 - 0.8)	4.16E-07	29	0.208	5571 (7)

Variant	Chr:position	Gene	Trait	Model	Age group	EA/NEA (EAF)	OR (CI)	P	I2 (%)	Het Q P	N (studies)
rs4025780	17:764038	NXN	doctors-diagnosed FA	main	children	A/G (0.2)	1.37 (1.21 - 1.55)	4.57E-07	12	0.339	10544 (8)
rs138021736	13:50028384	SETDB2	doctors-diagnosed FA	main	adults	T/A (0.03)	1.92 (1.49 - 2.47)	5.00E-07	0	0.792	226600 (3)
rs11643761	16:9065990	RP11-77H9.8, RP11-473I1.6	sensitization	main	children	A/T (0.09)	1.5 (1.28 - 1.76)	5.57E-07	0	0.757	7745 (8)
rs117937277	9:116941113	COL27A1	doctors-diagnosed FA	main	adults	C/A (0.02)	2.41 (1.71 - 3.4)	5.92E-07	0	0.984	226480 (3)
rs16952200	18:7602849	PTPRM	doctors-diagnosed FA	hay fever	children	C/A (0.03)	2.04 (1.54 - 2.7)	6.60E-07	0	0.606	9314 (6)
rs114560495	5:146894281	DPYSL3, JAKMIP2	self-reported FA	main, hay fever	adults	G/C (0.03)	1.46 (1.26 - 1.7)	6.74E-07	20	0.274	34378 (7)
rs2692192	3:180026087	GAPDHP36, RP11-420J11.1	doctors-diagnosed FA + sensitization	main	adults	A/G (0.05)	2.91 (1.91 - 4.44)	6.84E-07	0	0.497	3021 (3)
rs61648937	15:41407730	INO80	self-reported FA	main	adults	T/C (0.09)	1.21 (1.12 - 1.31)	7.02E-07	42	0.080	38307 (10)
rs12650891	4:94788391	ATOH1, RP11-363G15.2	doctors-diagnosed FA + sensitization	hay fever	adults	A/T (0.16)	1.9 (1.47 - 2.44)	7.43E-07	14	0.326	3717 (5)
rs62305340	4:84493126	AGPAT9	doctors-diagnosed FA	main	adults	G/A (0.23)	0.78 (0.71 - 0.86)	7.90E-07	0	0.916	229426 (7)
rs79989571	3:53474278	SNORA26, RP11-72H11.1	self-reported FA	hay fever	children	C/T (0.04)	1.85 (1.45 - 2.36)	8.15E-07	0	0.950	7201 (6)
rs10899967	10:44509338	LINC00841, AL512640.1	doctors-diagnosed FA	main	children	A/G (0.2)	1.33 (1.19 - 1.49)	8.23E-07	25	0.233	10544 (8)
rs10265041	7:151127104	RP4-555L14.4	self-reported FA	main, hay fever	adults	C/G (0.03)	1.43 (1.24 - 1.64)	8.47E-07	11	0.347	37326 (9)
rs73228469	12:97466262	RP11-541G9.1	doctors-diagnosed FA	main	adults	A/G (0.06)	1.53 (1.29 - 1.81)	8.52E-07	0	0.969	229296 (6)
rs12450646	17:5907793	WSCD1	self-reported FA	main	adults	T/C (0.36)	1.12 (1.07 - 1.18)	8.63E-07	0	0.930	39864 (12)
rs7108444	11:104857234	CASP4, CASP5	doctors-diagnosed FA + sensitization	main	children	G/C (0.15)	1.56 (1.31 - 1.86)	9.07E-07	0	0.698	5571 (7)
rs56296494	10:5918344	ANKRD16	sensitization	main	adults	A/G (0.04)	2.14 (1.58 - 2.9)	9.75E-07	15	0.316	3983 (4)

Alleles are reported as effect allele/other allele; Genome build = GRCh37 / hg19.

EA = Effect allele, NEA = Non effect allele, EAF = Effect allele frequency, OR = Odds ratio, CI = 95% confidence interval, I^2 = Heterogeneity estimate, Het Q P = Cochran's Q heterogeneity p-value, N (studies) = Number of participants included in the meta-analysis (number of studies included in the meta-analysis). If a SNP reached significance in both models (main + hay fever), the results for the main model are shown in the table. The other results can be found in Supplementary Table E6.

Table 2: Lead SNPs previously reported to be associated with allergies.

Variant	Chr:position	Gene	Trait	Model	Age group	EA/NEA (EAF)	Known associations	PMID
rs6007514	22:45640136	FAM118A	sensitization	main, hay fever	adults	T/A (0.48)	peanut allergy	29489655
rs2033784	15:67449660	SMAD3	doctors-diagnosed FA	main	adults	G/A (0.3)	asthma, atopic diseases, age of onset, allergic rhinitis	32296059, 29083406, 32603359, 30116036
rs66609926	2:61067286	AC010733.4	sensitization	main, hay fever	children	T/C (0.41)	atopic dermatitis	37794016

Alleles are reported as effect allele/other allele; Genome build = GRCh37 / hg19.
EA = Effect allele, NEA = Non effect allele, EAF = Effect allele frequency, OR = Odds ratio, CI = 95% confidence interval, I^2 = Heterogeneity estimate, Het Q P = Cochran's Q heterogeneity p-value, N = Sample size.

Table 3: Association results from discovery and replication stage in children.

						Discovery			Replication in food-specific sensitization phenotype[1]			Replication in oral food challenge phenotype[2]		
Variant	**Chr:position**	**Gene**	**Trait**	**Model**	**EA/NEA (EAF)**	**OR (CI)**	**P**	**N (studies)**	**OR (CI)**	**P**	**N (studies)**	**OR (CI)**	**P**	**N (studies)**
rs74991536	1:231163221	FAM89A	doctors-diagnosed FA	main, hay fever	C/T (0.98)	0.44 (0.32 - 0.61)	3.49E-07	9405 (6)	1.05 (0.88 - 1.25)	0.607	944 (2)	0.71 (0.48 - 1.05)	0.092	5403 (3)
rs10899967*	10:44509338	LINC00841, AL512640.1	doctors-diagnosed FA	main	A/G (0.2)	1.33 (1.19 - 1.49)	8.23E-07	10544 (8)	1.05 (0.98 - 1.13)	0.190	944 (2)	1.07 (0.93 - 1.24)	0.343	5850 (4)
rs7108444	11:104857234	CASP4, CASP5	doctors-diagnosed FA + sensitization	main	G/C (0.15)	1.56 (1.31 - 1.86)	9.07E-07	5571 (7)	1.00 (0.92 - 1.09)	0.996	492 (1)	0.93 (0.75 - 1.16)	0.539	4992 (2)
rs11645276	16:53092980	CHD9	doctors-diagnosed FA + sensitization	main	C/T (0.4)	0.68 (0.59 - 0.79)	3.07E-07	5571 (7)	1.00 (0.94 - 1.08)	0.921	492 (1)	0.95 (0.81 - 1.12)	0.555	4992 (2)
rs11643761	16:9065990	RP11-77H9.8, RP11-473I1.6	sensitization	main	A/T (0.09)	1.5 (1.28 - 1.76)	5.57E-07	7745 (8)	1.06 (0.96 - 1.18)	0.252	492 (1)	1.06 (0.81 - 1.38)	0.676	4992 (2)
rs4025780	17:764038	NXN	doctors-diagnosed FA	main	A/G (0.2)	1.37 (1.21 - 1.55)	4.57E-07	10544 (8)	0.97 (0.9 - 1.05)	0.404	492 (1)	1.1 (0.91 - 1.33)	0.336	4992 (2)
rs16952200	18:7602849	PTPRM	doctors-diagnosed FA	hay fever	C/A (0.03)	2.04 (1.54 - 2.7)	6.60E-07	9314 (6)	1.01 (0.87 - 1.17)	0.916	944 (2)	0.93 (0.65 - 1.33)	0.694	4616 (2)
rs1022311	2:180555884	ZNF385B	doctors-diagnosed FA	main, hay fever	T/C (0.1)	1.48 (1.28 - 1.72)	1.80E-07	10544 (8)	0.98 (0.89 - 1.09)	0.729	492 (1)	1.03 (0.81 - 1.30)	0.779	5442 (3)
rs74531285	2:197132359	HECW2	doctors-diagnosed FA	main	T/C (0.02)	2.42 (1.75 - 3.36)	1.28E-07	8497 (5)	0.91 (0.71 - 1.18)	0.489	492 (1)	1.29 (0.78 - 2.15)	0.320	4992 (2)
rs76119799	2:212415241	ERBB4	self-reported FA	main, hay fever	T/G (0.05)	0.52 (0.41 - 0.67)	3.92E-07	8627 (6)	1.06 (0.91 - 1.23)	0.472	492 (1)	0.92 (0.62 - 1.37)	0.682	4992 (2)
rs78609709	2:53770433	GPR75-ASB3	doctors-diagnosed	hay fever	C/A (0.04)	2.4 (1.73 - 3.32)	1.40E-07	5188 (6)	1.14 (0.99 - 1.3)	0.064	944 (2)	1.01 (0.75 - 1.36)	0.955	5403 (3)

						Discovery			Replication in food-specific sensitization phenotype[1]			Replication in oral food challenge phenotype[2]		
Variant	**Chr:position**	**Gene**	**Trait**	**Model**	**EA/NEA (EAF)**	**OR (CI)**	**P**	**N (studies)**	**OR (CI)**	**P**	**N (studies)**	**OR (CI)**	**P**	**N (studies)**
			FA + sensitization											
rs73174808	3:177288324	LINC00578	self-reported FA	main	C/A (0.06)	1.59 (1.33 - 1.91)	4.02E-07	12883 (9)	0.98 (0.85 - 1.12)	0.717	492 (1)	0.83 (0.57 - 1.21)	0.331	4992 (2)
rs79989571	3:53474278	SNORA26, RP11-72H11.1	self-reported FA	hay fever	C/T (0.04)	1.85 (1.45 - 2.36)	8.15E-07	7201 (6)	1.02 (0.9 - 1.16)	0.759	944 (2)	0.98 (0.72 - 1.33)	0.887	5403 (3)
rs62248296	3:68324177	FAM19A1	self-reported FA	hay fever	G/A (0.19)	1.44 (1.25 - 1.66)	3.43E-07	6651 (6)	1.04 (0.95 - 1.14)	0.366	492 (1)	0.85 (0.69 - 1.06)	0.148	4992 (2)
rs2055684	3:69108316	UBA3	doctors-diagnosed FA + sensitization	main, hay fever	A/T (0.47)	0.7 (0.61 - 0.8)	4.16E-07	5571 (7)	1.02 (0.96 - 1.09)	0.525	492 (1)	1.08 (0.94 - 1.24)	0.273	5444 (3)
rs6833463	4:21244175	KCNIP4	doctors-diagnosed FA + sensitization	main	A/G (0.24)	1.5 (1.3 - 1.74)	5.05E-08	5571 (7)	0.97 (0.85 - 1.12)	0.689	943 (2)	1 (0.88 - 1.15)	0.954	5854 (4)
rs55681581	5:126981185	PRRC1, CTXN3	self-reported FA	main	T/C (0.15)	1.37 (1.22 - 1.55)	2.74E-07	12514 (9)	1.02 (0.94 - 1.1)	0.689	492 (1)	0.87 (0.72 - 1.04)	0.128	5428 (3)

[1]studies included: GENEVA, CLARA&CLAUS

[2]studies included: GENEVA, GOFA, MAAS, HealtNuts

*following proxy was used in HealthNuts: rs10899968.

Alleles are reported as effect allele/other allele; Genome build = GRCh37 / hg19.

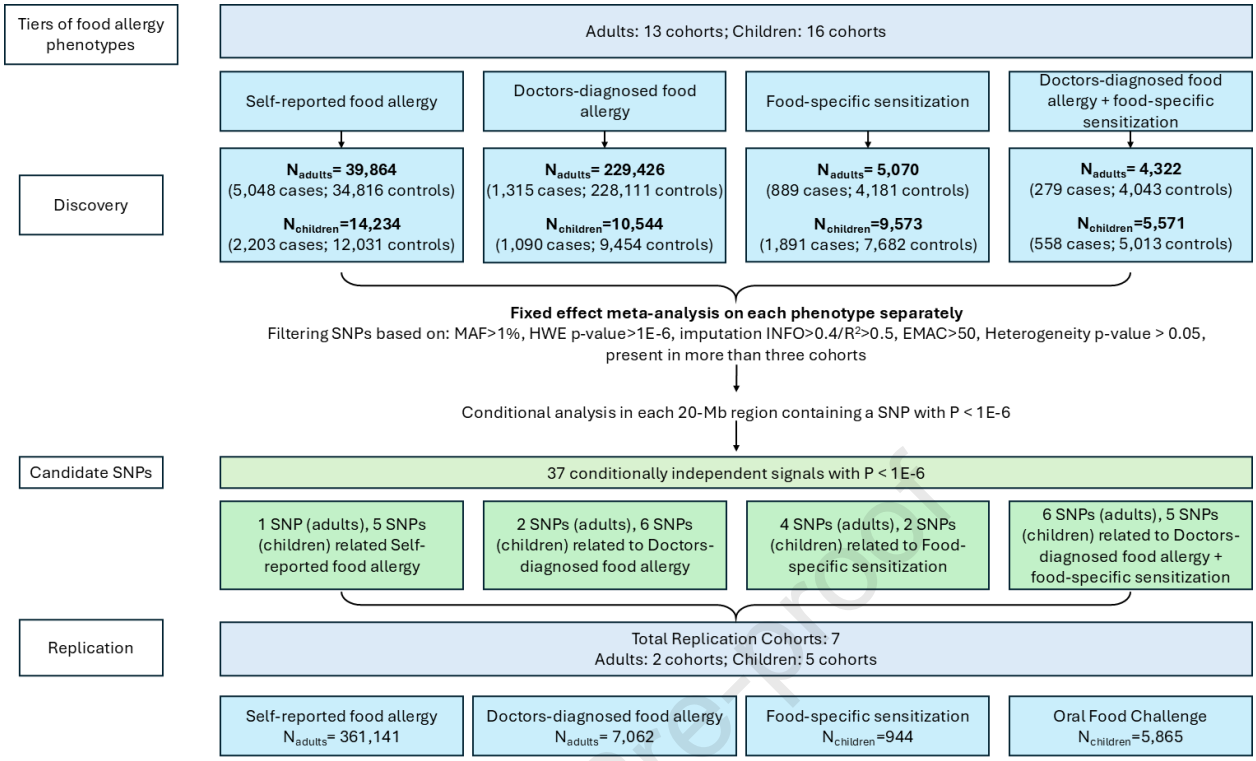
EA = Effect allele, NEA = Non effect allele, EAF = Effect allele frequency, OR = Odds ratio, CI = 95% confidence interval, N (studies) = Number of participants included in the meta-analysis (number of studies included in the meta-analysis).

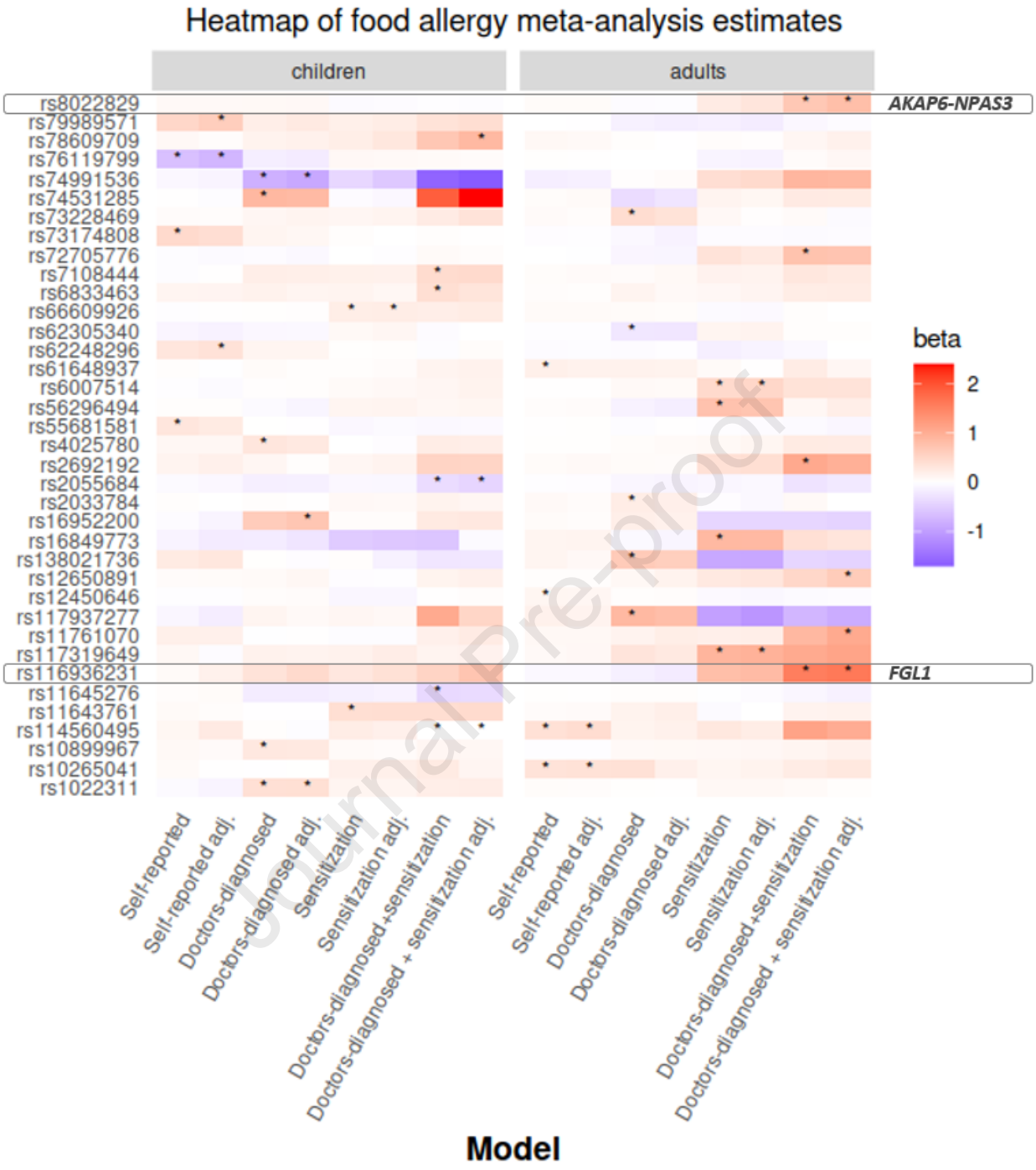
Table 4: Association results from discovery and replication stage in adults.

						Discovery			Replication in self-reported food allergy phenotype[1]			Replication in doctors-diagnosed food allergy phenotype[2]		
Variant	**Chr:position**	**Gene**	**Trait**	**Model**	**EA/NEA (EAF)**	**OR (CI)**	**P**	**N (studies)**	**OR (CI)**	**P**	**N (studies)**	**OR (CI)**	**P**	**N (studies)**
rs16849773	1:202204213	LGR6	sensitization	main	A/G (0.02)	2.4 (1.72 - 3.34)	2.46E-07	3056 (3)	0.99 (0.99 - 1.00)	0.44	361141 (1)	2.38 (1.14 - 4.99)	0.02	7062 (1)
rs117319649	10:47668777	ANTXRL	sensitization	main, hay fever	T/G (0.04)	2.52 (1.79 - 3.57)	1.58E-07	3247 (3)	NA	NA	NA	NA	NA	NA
rs56296494	10:5918344	ANKRD16	sensitization	main	A/G (0.04)	2.14 (1.58 - 2.9)	9.75E-07	3983 (4)	1.00 (0.99 - 1.00)	0.62	361141 (1)	1.11 (0.47 - 2.61)	0.81	7062 (1)
rs73228469	12:97466262	RP11-541G9.1	doctors-diagnosed FA	main	A/G (0.06)	1.53 (1.29 - 1.81)	8.52E-07	229296 (6)	0.99 (0.99 - 1.00)	0.38	361141 (1)	1.4 (0.7 - 2.82)	0.34	7062 (1)
rs138021736	13:50028384	SETDB2	doctors-diagnosed FA	main	T/A (0.03)	1.92 (1.49 - 2.47)	5.00E-07	226600 (3)	0.99 (0.99 - 1.00)	0.53	361141 (1)	1.76 (0.75 - 4.09)	0.19	7062 (1)
rs8022829	14:33397346	AKAP6, NPAS3	doctors-diagnosed FA + sensitization	main, hay fever	A/G (0.09)	1.99 (1.52 - 2.62)	7.74E-07	4050 (5)	1.00 (0.99 - 1.00)	0.07	361141 (1)	0.72 (0.42 - 1.23)	0.23	7062 (1)
rs61648937	15:41407730	INO80	self-reported FA	main	T/C (0.09)	1.21 (1.12 - 1.31)	7.02E-07	38307 (10)	0.99 (0.99 - 1.00)	0.69	361141 (1)	0.95 (0.58 - 1.56)	0.84	7062 (1)
rs12450646	17:5907793	WSCD1	self-reported FA	main	T/C (0.36)	1.12 (1.07 - 1.18)	8.63E-07	39864 (12)	1.00 (0.99 - 1.00)	0.79	361141 (1)	1.08 (0.79 - 1.49)	0.62	7062 (1)
rs2692192	3:180026087	GAPDHP36, RP11-420J11.1	doctors-diagnosed FA + sensitization	main	A/G (0.05)	2.91 (1.91 - 4.44)	6.84E-07	3021 (3)	1.00 (0.99 - 1.00)	0.21	361141 (1)	1.21 (0.61 - 2.4)	0.59	7062 (1)
rs72705776	4:180911393	RP11-774G5.1, RP11-751A18.1	doctors-diagnosed FA + sensitization	main	T/C (0.09)	2.13 (1.61 - 2.83)	1.66E-07	4050 (5)	0.99 (0.99 - 1.00)	0.41	361141 (1)	1.17 (0.69 - 1.99)	0.56	7062 (1)
rs62305340	4:84493126	AGPAT9	doctors-diagnosed FA	main	G/A (0.23)	0.78 (0.71 - 0.86)	7.90E-07	229426 (7)	1.00 (0.99 - 1.00)	0.50	361141 (1)	0.83 (0.57 - 1.2)	0.32	7062 (1)

rs12650891	4:94788391	ATOH1, RP11-363G15.2	doctors-diagnosed FA + sensitization	hay fever	A/T (0.16)	1.9 (1.47 - 2.44)	7.43E-07	3717 (5)	1.00 (0.99 - 1.00)	0.68	361141 (1)	1.2 (0.79 - 1.83)	0.40	7062 (1)
rs114560495	5:146894281	DPYSL3, JAKMIP2	self-reported FA	main, hay fever	G/C (0.03)	1.46 (1.26 - 1.7)	6.74E-07	34378 (7)	1.00 (0.99 - 1.00)	0.99	361141 (1)	1.16 (0.48 - 2.8)	0.74	7062 (1)
rs10265041	7:151127104	RP4-555L14.4	self-reported FA	main, hay fever	C/G (0.03)	1.43 (1.24 - 1.64)	8.47E-07	37326 (9)	1.00 (0.99 - 1.00)	0.24	361141 (1)	1.33 (0.58 - 3.03)	0.50	7062 (1)
rs11761070	7:24587280	MPP6, RNU6-1103P	doctors-diagnosed FA + sensitization	hay fever	C/A (0.07)	2.89 (1.96 - 4.26)	8.70E-08	3031 (3)	1.00 (1 - 1.00)	0.05	361141 (1)	0.65 (0.35 - 1.23)	0.18	7062 (1)
rs116936231	8:17753408	FGL1	doctors-diagnosed FA + sensitization	main, hay fever	T/C (0.02)	4.76 (2.77 - 8.18)	1.62E-08	3047 (3)	0.99 (0.99 - 1.00)	0.14	361141 (1)	0.44 (0.13 - 1.44)	0.17	7062 (1)
rs117937277	9:116941113	COL27A1	doctors-diagnosed FA	main	C/A (0.02)	2.41 (1.71 - 3.4)	5.92E-07	226480 (3)	0.99 (0.99 - 1.00)	0.76	361141 (1)	0.48 (0.18 - 1.26)	0.14	7062 (1)

[1]studies included: UK Biobank.
[2]studies included: EXCEED.
*following proxy was used in HealthNuts: 10:44509620.
Alleles are reported as effect allele/other allele; Genome build = GRCh37 / hg19.
EA = Effect allele, NEA = Non effect allele, EAF = Effect allele frequency, OR = Odds ratio, CI = 95% confidence interval, N (studies) = Number of participants included in the meta-analysis (number of studies included in the meta-analysis).




Heatmap of food allergy meta-analysis estimates
children
adults
rs8022829
rs79989571
rs78609709
rs76119799
rs74991536
rs74531285
rs73228469
rs73174808
rs72705776
rs7108444
rs6833463
rs66609926
rs62305340
rs62248296
rs61648937
rs6007514
rs56296494
rs55681581
rs4025780
rs2692192
rs2055684
rs2033784
rs16952200
rs16849773
rs138021736
rs12650891
rs12450646
rs117937277
rs11761070
rs117319649
rs116936231
rs11645276
rs11643761
rs114560495
rs10899967
rs10265041
rs1022311
AKAP6-NPAS3
FGL1
beta
2
1
0
-1
Self-reported
Self-reported adj.
Doctors-diagnosed
Doctors-diagnosed adj.
Sensitization
Sensitization adj.
Doctors-diagnosed +sensitization
Doctors-diagnosed + sensitization adj.
Model