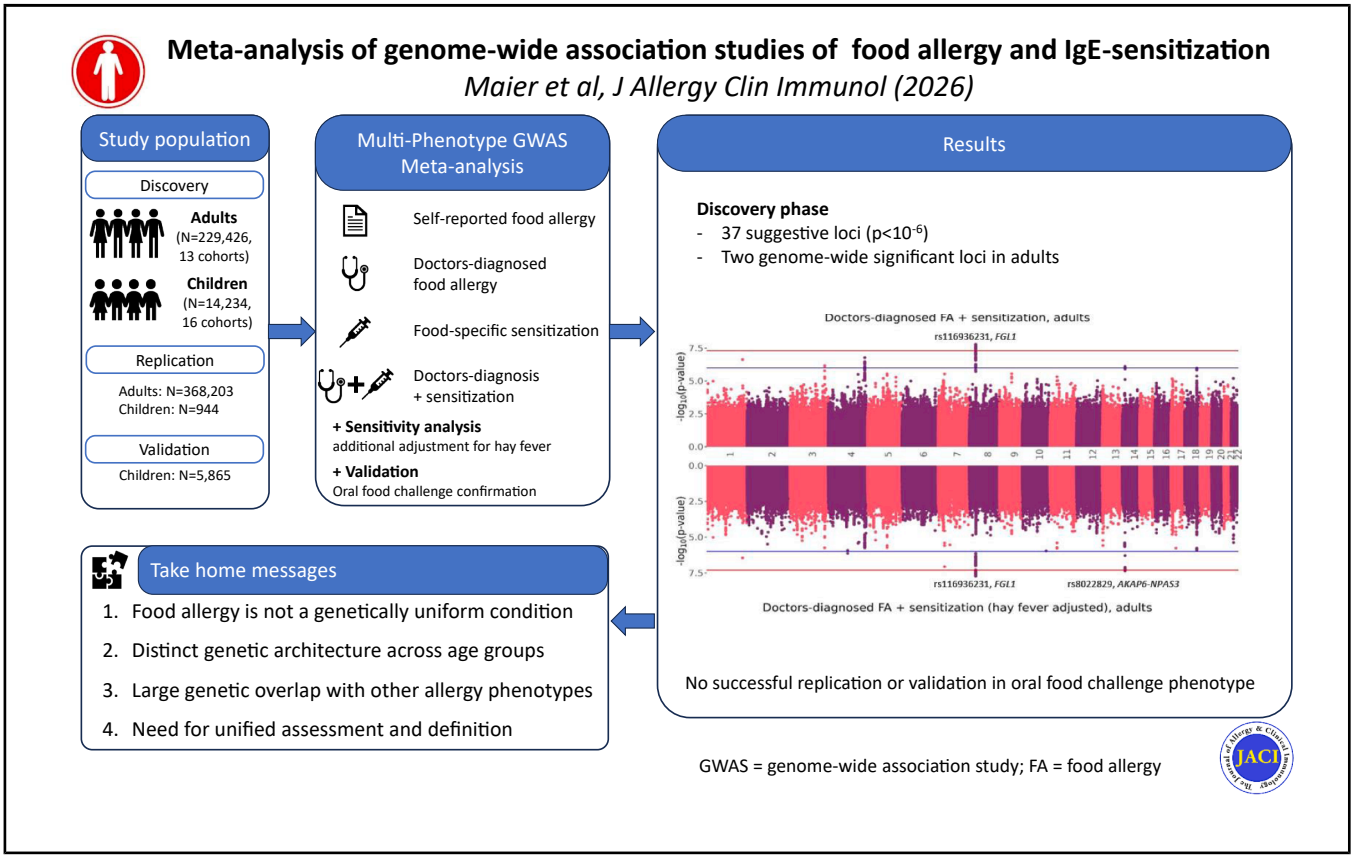
Meta-analysis of genome-wide association studies of food allergy and IgE sensitization

Lisa Maier, MSc, Yidan Sun, MSc, Jaanika Kronberg, PhD, Erik Abner, PhD, Kayesha Coley, PhD, Ingo Marenholz, PhD, et al

GRAPHICAL ABSTRACT



Capsule summary: This genome-wide association study meta-analysis identified 37 single nucleotide polymorphisms suggestively associated with food allergy (FA), revealing genetic differences across age groups and FA definitions, alongside overlaps with other atopic diseases, providing valuable insights into genetic susceptibility to FA.

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

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

Objective: We sought to identify novel FA risk loci by conducting a genome-wide association study meta-analysis in children and adults by using a multiphenotype approach to ensure a good trade-off between sufficient sample size and valid FA definitions.

Methods: Analyses were conducted separately in children and adults on the basis of the following FA phenotypes: self-report, doctor diagnosis, food-specific sensitization, and doctor diagnosis plus food-specific sensitization. A meta-analysis was performed of genome-wide association studies from up to 16 cohorts of people of European ancestry including 229,426 adults and 14,234 children. 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: Thirty-seven single nucleotide polymorphisms met suggestive significance ($P < 1 \times 10^{-6}$), with two reaching genome-wide significance: rs116936231 *(FGL1)* in adult doctor-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 3 single nucleotide polymorphisms previously reported for FA and atopic disease.

Conclusion: This study identified 37 single nucleotide polymorphisms suggestively associated with FA and demonstrated genetic differences across phenotypes. It highlights the need for a unified FA definition and sheds light on FA's shared genetic architecture with allergies. (J Allergy Clin Immunol 2026;■■■:■■■-■■■.)

Key words: *Genome-wide association study, food allergy, meta-analysis, specific IgE, hay fever, sensitization, epidemiology*

Food allergy (FA) is a complex disease defined as an adverse response of the immune system to innocuous food proteins mediated by specific IgE.[1] FA prevalence, as verified by the diagnostic reference 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 6 times higher.[4] Differences in the manifestation of the allergic reactions complicate an accurate diagnosis.[5] Because 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 specific IgE measurements or skin prick tests 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%.[7] 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.[8-14] These variants account for a limited proportion of heritability,[8] which suggests that further risk variants remain to be identified. Sufficiently powered large-scale GWAS meta-analyses are currently lacking,[7,15] but such studies would allow detection of variants with smaller effect sizes and/or allele frequencies. Furthermore, most genetic studies of FA have focused on pediatric patients whose disease is characterized

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Abbreviations used
CI: Confidence interval
eQTL: Expression quantitative trait locus
FA: Food allergy
GWAS: Genome-wide association studies
LD: Linkage disequilibrium
LDSC: LD score regression
OFC: Oral food challenge
OR: Odds ratio
SNP: Single nucleotide polymorphism

by comprehensive clinical phenotyping and are often targeted to specific allergens.[9,12,14] The etiology of food allergies exhibits notable differences between children and adults because mechanisms of sensitization, allergens, and clinical presentation vary by age.[16] In adults, pollen sensitization is highly prevalent and contributes to secondary FA due to allergen cross-reactivity.[6,17,18]

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 single nucleotide polymorphisms (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 as a result of 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 being a primary sensitization to apple itself. This reaction is then defined as pollen-FA syndrome.[19]

METHODS

The overview of the study design can be found in Fig 1. Study protocols were approved by the local ethics committees of the respective cohorts (see the Methods section in this article's Online Repository available at www.jacionline.org).

Phenotype definition

Cases were defined as occurring in patients who ever (1) self-reported any FA (compared to those never reporting any FA), (2) self-reported a doctor-diagnosed FA (compared to those never reporting a doctor-diagnosed FA), (3) showed positive food-specific sensitization measured via skin prick test or specific IgEs (≥0.35 kU_A/L) (compared to those without food-specific sensitization), and (4) reported a doctor-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 the Methods section in the Online Repository and sample sizes per phenotype in Table E1 in the Online Repository available at www.jacionline.org.

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 Methods section in the Online Repository. 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 Table E2 in the Online Repository available at www.jacionline.org. 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 while at the same time it obscure shared genetic effects.

Standardized quality control of cohort summary statistics included checks for completeness, formatting, duplicates, monomorphic SNPs, nonsense values, Hardy-Weinberg violations (Hardy-Weinberg equilibrium $P < 1e^{-6}$),[20] low-imputation-quality variants ($r^2 \leq 0.5$, INFO score ≤ 0.4),[21] low estimated minor allele count (EMAC = (2 × N × minor allele frequency × imputation quality score) ≤ 50),[22] and minor allele frequency ≤ 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 underwent meta-analysis by an inverse-variance weighted fixed effect model with genomic control using GWAMA.[23] Meta-analyses were conducted by FA phenotype and age group (children [<18 years old] and adults). Heterogeneity between studies was assessed by the Cochran Q statistic and I^2. Variants with Cochran heterogeneity of $P \leq .05$ and present in fewer than 3 studies were excluded.

Identification of risk variants and lead SNPs

FUMA v1.5.2[24] was used to identify lead SNPs in candidate regions. SNPs meeting suggestive significance ($P < 1 \times 10^{-6}$) were first clumped using the 1000 Genomes Project 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 $r^2 \geq 0.1$) with previously published variants associated with FA or other allergic diseases (see Table E3 in the Online Repository available at www.jacionline.org). 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 threshold of $P < .05$.

Replication

Identified lead variants from the discovery were taken forward for replication. External replication using additional cohorts was performed in (1) self-reported FA in adults, (2) doctor-diagnosed FA in adults, and (3) food-specific sensitization in children.

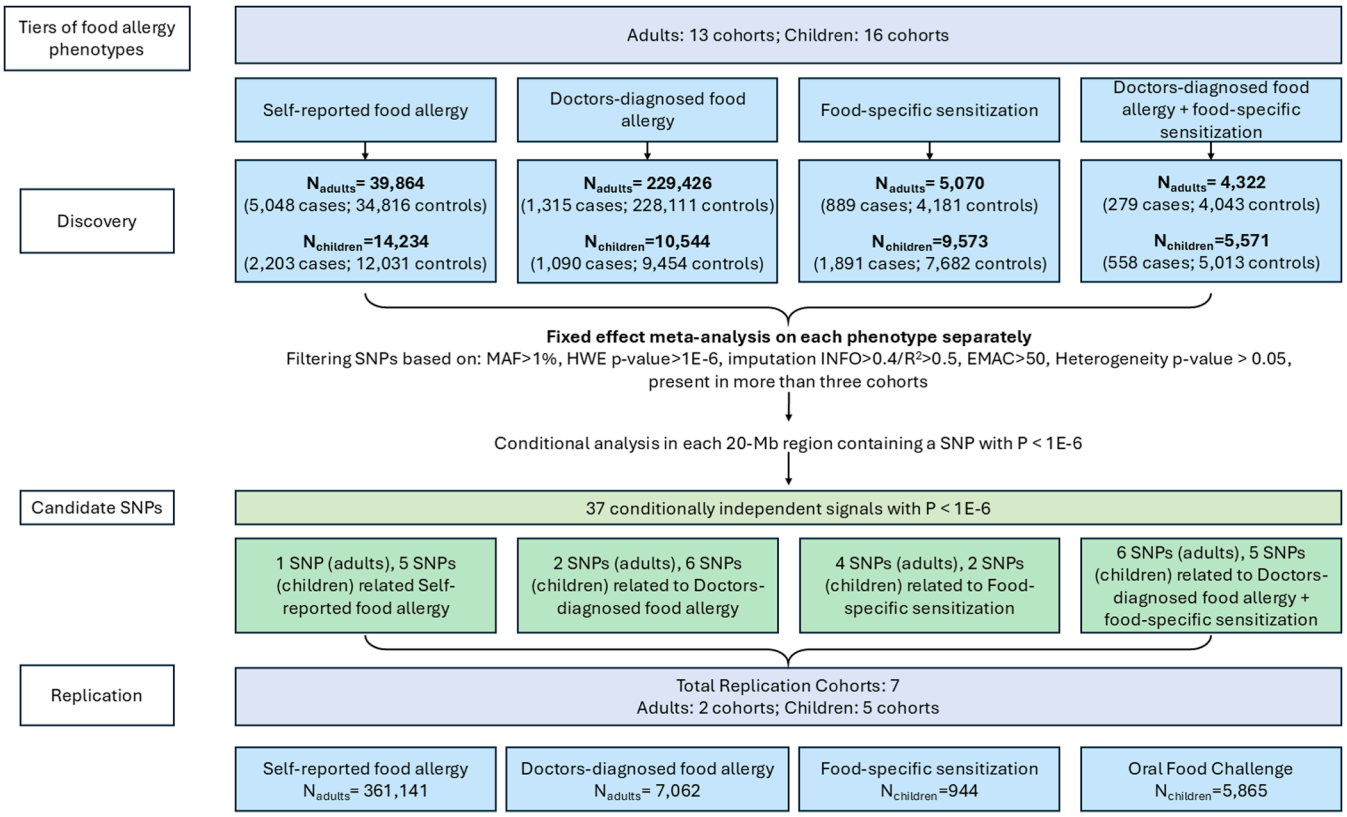

FIG 1. Overview of GWAS meta-analysis and replication study design.

Additionally, a validation study was carried out in an independent sample of children with OFC-confirmed FA (see Tables E2 and E4 in the Online Repository available at www.jacionline.org) and a Bonferroni-corrected alpha threshold applied.

Conditional analysis

Independent association signals were identified among the significant genetic variants through conditional analyses, performed by GCTA-conditional and joint analysis and summary statistics from the meta-analysis and LD correlations between SNPs. A LD correlation matrix was estimated on the basis of a subgroup of the Lifelines cohort that was not used for meta-analysis.[25] We excluded one individual from each pair with a genetic relatedness (identical by descent) above 0.1875, retaining 9,027 unrelated individuals in the Lifelines subcohort. LD correlations were disregarded for SNPs over 20 Mb apart or on different chromosomes to avoid sample overlap in subsequent analyses. A suggestive significance threshold ($P < 1 \times 10^{-6}$) was applied for the SNP selection.

LD score regression for heritability estimation

We used the LD score regression (LDSC) method of LDSC v1.0.1 software[26] to determine the SNP-based heritability (h^2_{SNP}) for each FA phenotype. The 95% confidence intervals (CIs) were calculated by the Wald method. This analysis was conducted by using summary statistics from the discovery meta-analyses. Heritability calculations were adjusted to a liability scale, considering a population prevalence of 0.1,[27] with sample prevalence calculated for each FA phenotype separately. LDSC estimates the genetic heritability contributed by common variants genome-wide, incorporating both significant and subthreshold SNPs.

Genetic correlations were assessed using all available 1,639 traits by CTG-VL.[28] We identified nominally significant genetic correlations ($P < .05$) and applied a Bonferroni-corrected alpha threshold of 0.05/1639 ($P < 3.05 \times 10^{-5}$) 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 between −1 and 1.

Functional annotations and gene mapping

MAGMA (Multi-marker Analysis of GenoMic Annotation) v1.08 enrichment analysis using RNA sequencing data from GTEx v8[29] 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 ($r^2 \geq 0.6$) with them were annotated by FUMA v1.5.2.[24] 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 ±10 kb using ANNOVAR annotation), expression quantitative trait locus (eQTL) mapping (linking SNPs to tissue-specific eQTLs with a false discovery rate of <.05 within ±1 Mb as *cis*-eQTLs), and chromatin interaction mapping (identifying long-range

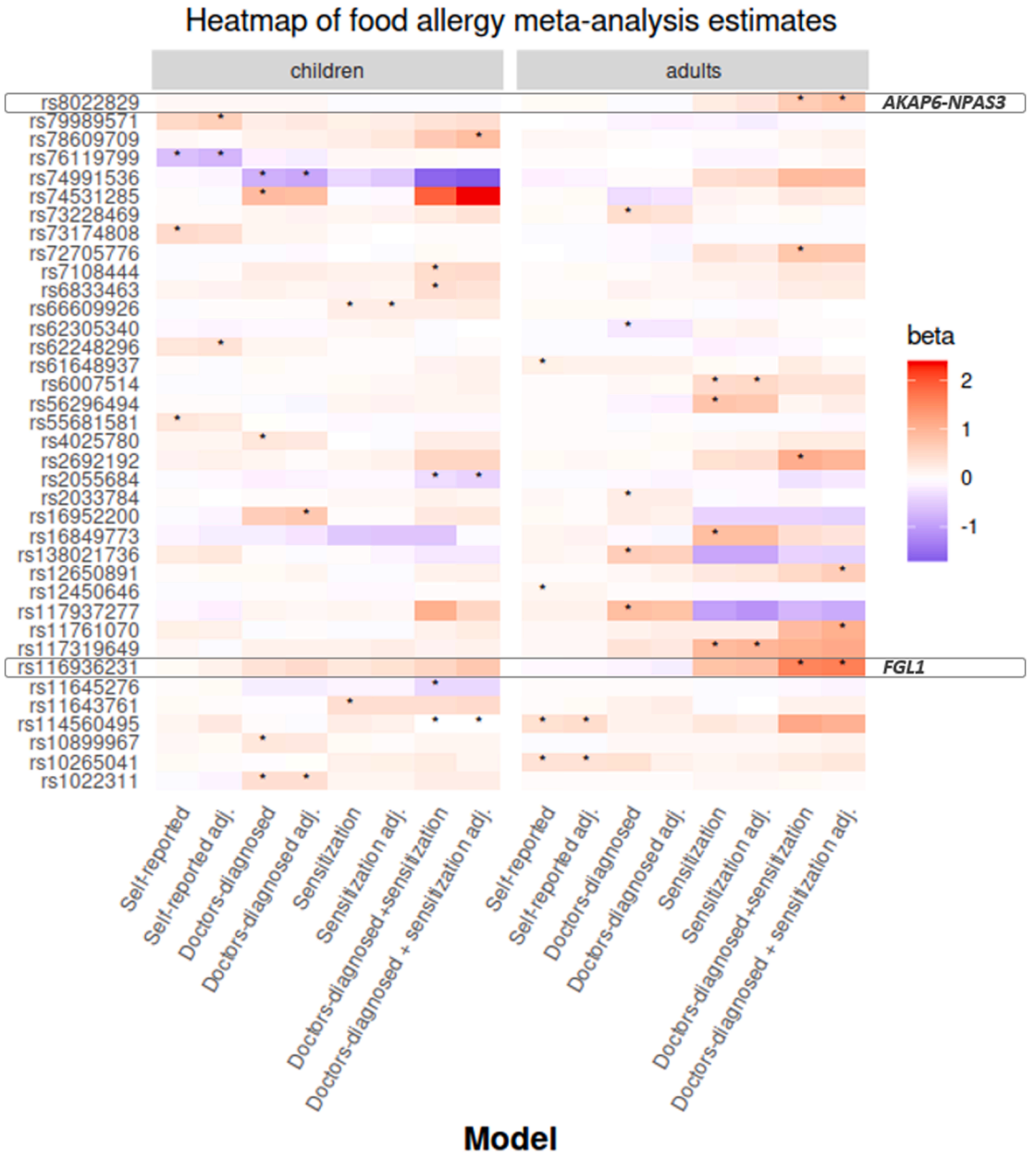

FIG 2. Heat map of effect estimates from GWAS meta-analyses by phenotype and age group for 37 lead SNPs. Lead SNPs are indicated on y-axis, and results per phenotype and model are displayed on x-axis. Asterisks indicate trait where significance threshold ($P < 1 \times 10^{-6}$) was passed in discovery.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

interactions by mapping variants to genes with promoter regions overlapping significant chromatin interactions, defined as 250 bp upstream and 500 bp downstream of the transcription start site, with a false discovery rate 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 underwent meta-analysis separately by age group and phenotype: self-reported (5,048 adults and 2,203 children), doctor-diagnosed (1,315 adults and 1,090 children), and food-specific sensitization (889 adults and 1,891 children), and reported FA plus food-specific sensitization (279 adults and 558 children). Numbers per study are depicted in Table E1. There was no evidence for population stratification, with genomic inflation factor λ ranging from 0.93 to 1.00 (see Table E5 and Fig E1 in the Online Repository available at www.jacionline.org). Fig 2 shows the 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 doctor-diagnosed FA plus food-specific

sensitization in adults (4,322 participants, 4,296 with hay fever) revealed two novel loci of genome-wide significance ($P < 5 \times 10^{-8}$): rs116936231 near *FGL1* (main model: odds ratio [OR] = 4.76, $P = 1.62 \times 10^{-8}$; hay fever–adjusted model: OR = 5.03, $P = 1.86 \times 10^{-8}$) and rs8022829 near *AKAP6-NPAS3* (OR = 2.23, $P = 4.31 \times 10^{-8}$), with the latter being significant only in the hay fever–adjusted model (Table I, Fig 3). The forest plot showed consistent direction and magnitude of the effect across studies (see Fig E4 in the Online Repository). Moreover, a further 35 signals yielded suggestive significance ($P < 1 \times 10^{-6}$) (see Table E6 and Fig E2 in the Online Repository), two of which were removed from the lead SNPs eligible for replication because of significant between-study heterogeneity (Cochran heterogeneity $P < .05$). The conditional analysis revealed no additional independent associations (see Fig E5 in the Online Repository). When we used a more stringent phenotype definition, we identified stronger genetic signals.

Overlap of lead SNPs with other allergic traits. Heat maps were used to visually compare the effects of previously identified allergy-associated SNPs related to FA ($P < .05$) across the FA meta-analyses (see Fig E6 in the Online Repository available at www.jacionline.org). In total, 229 of 472 SNPs showed association with more than one FA phenotype, including variants in the *FLG* and *HLA* loci. Three of the lead SNPs have been previously reported to be associated with allergy phenotypes on the basis of LD calculation (Table II). The variant rs2033784 near *SMAD3* is in strong LD ($r^2 = 0.7$), with variants previously associated with asthma,[30] atopic disease,[31] allergic rhinitis,[32] and age at allergy onset.[33] Another variant in LD with rs66609926 ($r^2 = 0.12$) near *AC010733.4* has been associated with atopic dermatitis.[34] Additionally, rs998706 within a ±1 Mb window with our lead variant rs6007514 has been associated with peanut allergy.[35] Because rs6007514 is not in the 1000 Genomes Project reference panel we used, it was not possible to calculate LD, but the physical proximity and assignment to the same gene, *FAM118A,* suggests that 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 ($P < .01$), suggesting a shared genetic basis between allergic conditions in FA (see Tables E7 and E8 in the Online Repository available at www.jacionline.org).

Furthermore, we compared previously identified FA related variants with our findings. Eight SNPs in children and 6 SNPs in adults showed nominal significance ($P < .05$) 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 of a Japanese cohort (see Tables E9 and E10 in the Online Repository available at www.jacionline.org).

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

Comparison of association across main and hay fever–adjusted models

ORs 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 (see Fig E7 in the Online Repository available at www.jacionline.org).

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 was significant (see Fig E8 in the Online Repository available at www.jacionline.org), 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 doctor-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 because of established clinical differences, and any contrasts observed reflect differences across these age-defined study populations rather than direct comparisons of age at disease onset.

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[36] (N_{total} = 361,141), doctor-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, and 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 III). 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 doctor-diagnosed FA showed 68.8% consistent effect directions (Table IV). 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 (Tables III and IV). 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 by 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

TABLE I. Novel suggestive and genome-wide significant lead SNPs from discovery meta-analyses

Variant	Chr:position	Gene	Trait	Model
rs116936231	8:17753408	*FGL1*	Doctor-diagnosed FA + sensitization	Main, hay fever
rs8022829	14:33397346	*AKAP6, NPAS3*	Doctor-diagnosed FA + sensitization	Main, hay fever
rs6833463	4:21244175	*KCNIP4*	Doctor-diagnosed FA + sensitization	Main
rs11761070	7:24587280	*MPP6, RNU6-1103P*	Doctor-diagnosed FA + sensitization	Hay fever
rs74531285	2:197132359	*HECW2*	Doctor-diagnosed FA	Main
rs78609709	2:53770433	*GPR75-ASB3*	Doctor-diagnosed FA + sensitization	Hay fever
rs117319649	10:47668777	*ANTXRL*	Sensitization	Main, hay fever
rs72705776	4:180911393	*RP11-774G5.1, RP11-751A18.1*	Doctor-diagnosed FA + sensitization	Main
rs1022311	2:180555884	*ZNF385B*	Doctor-diagnosed FA	Main, hay fever
rs16849773	1:202204213	*LGR6*	Sensitization	Main
rs55681581	5:126981185	*PRRC1, CTXN3*	Self-reported FA	Main
rs11645276	16:53092980	*CHD9*	Doctor-diagnosed FA + sensitization	Main
rs62248296	3:68324177	*FAM19A1*	Self-reported FA	Hay fever
rs74991536	1:231163221	*FAM89A*	Doctor-diagnosed FA	Main, hay fever
rs76119799	2:212415241	*ERBB4*	Self-reported FA	Main, hay fever
rs73174808	3:177288324	*LINC00578*	Self-reported FA	Main
rs2055684	3:69108316	*UBA3*	Doctor-diagnosed FA + sensitization	Main, hay fever
rs4025780	17:764038	*NXN*	Doctor-diagnosed FA	Main
rs138021736	13:50028384	*SETDB2*	Doctor-diagnosed FA	Main
rs11643761	16:9065990	*RP11-77H9.8, RP11-473I1.6*	Sensitization	Main
rs117937277	9:116941113	*COL27A1*	Doctor-diagnosed FA	Main
rs16952200	18:7602849	*PTPRM*	Doctor-diagnosed FA	Hay fever
rs114560495	5:146894281	*DPYSL3, JAKMIP2*	Self-reported FA	Main, hay fever
rs2692192	3:180026087	*GAPDHP36, RP11-420J11.1*	Doctor-diagnosed FA + sensitization	Main
rs61648937	15:41407730	*INO80*	Self-reported FA	Main
rs12650891	4:94788391	*ATOH1, RP11-363G15.2*	Doctor-diagnosed FA + sensitization	Hay fever
rs62305340	4:84493126	*AGPAT9*	Doctor-diagnosed FA	Main
rs79989571	3:53474278	*SNORA26, RP11-72H11.1*	Self-reported FA	Hay fever
rs10899967	10:44509338	*LINC00841, AL512640.1*	Doctor-diagnosed FA	Main
rs10265041	7:151127104	*RP4-555L14.4*	Self-reported FA	Main, hay fever
rs73228469	12:97466262	*RP11-541G9.1*	Doctor-diagnosed FA	Main
rs12450646	17:5907793	*WSCD1*	Self-reported FA	Main
rs7108444	11:104857234	*CASP4, CASP5*	Doctor-diagnosed FA + sensitization	Main
rs56296494	10:5918344	*ANKRD16*	Sensitization	Main

Alleles are reported as effect allele/other allele. Genome build is GRCh37/hg19. If SNP reached significance in both models (main + hay fever), results for main model are shown. Other results can be found in Table E6. *EA,* Effect allele; *EAF,* EA frequency; Het Q P, Cochran *Q* heterogeneity *P* value; *NEA,* non-EA.

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 (see Table E11 in the Online Repository available at www.jacionline.org). For the more objectively defined phenotype that is 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 doctor-diagnosed FA phenotype in adults (see Fig E9 in the Online Repository available at www.jacionline.org). In children, brain, heart, and pituitary tissues were significantly enriched across phenotypes (Fig E9). Gene sets of the prefrontal cortex were significant in the doctor-diagnosed FA phenotype in children with hay fever adjustment (see Table E12 in the Online Repository). Gene-based tests did not show any significant results (see Figs E10 and E11 in the Online Repository).

Genes were mapped according to age group, phenotype, and model according to their position, eQTL, and chromatin interaction (see Tables E13 to E27 in the Online Repository available at www.jacionline.org). There was no overlap of genes across the phenotypes for adults within the main and hay fever–adjusted models (see Fig E12, *C* and *D,* in the Online Repository). In children, there were two overlapping genes in the hay fever–adjusted meta-analyses (Fig E12, *B*). Both genes, *EOGT* and *FAM19A1,* were mapped by chromatin interaction in the self-reported and doctor-diagnosed plus food-specific sensitization phenotype and are protein-coding genes located on chromosome 3. *FAM19A1* has a probability of having a loss-of-function intolerant score of

Age group	EA/NEA (EAF)	OR (95% CI)	P	I^2 (%)	Het Q P	No. participants (no. studies)
Adults	T/C (0.02)	4.76 (2.77-8.18)	1.62E-08	0	.757	3047 (3)
Adults	A/G (0.09)	2.23 (1.68-2.98)	4.31E-08	0	.628	4026 (5)
Children	A/G (0.24)	1.5 (1.3-1.74)	5.05E-08	0	.819	5571 (7)
Adults	C/A (0.07)	2.89 (1.96-4.26)	8.70E-08	0	.764	3031 (3)
Children	T/C (0.02)	2.42 (1.75-3.36)	1.28E-07	15	.321	8497 (5)
Children	C/A (0.04)	2.4 (1.73-3.32)	1.40E-07	26	.236	5188 (6)
Adults	T/G (0.04)	2.52 (1.79-3.57)	1.58E-07	0	.780	3247 (3)
Adults	T/C (0.09)	2.13 (1.61-2.83)	1.66E-07	35	.190	4050 (5)
Children	T/C (0.1)	1.48 (1.28-1.72)	1.80E-07	7	.374	10,544 (8)
Adults	A/G (0.02)	2.4 (1.72-3.34)	2.46E-07	31	.237	3056 (3)
Children	T/C (0.15)	1.37 (1.22-1.55)	2.74E-07	0	.526	12,514 (9)
Children	C/T (0.4)	0.68 (0.59-0.79)	3.07E-07	0	.844	5571 (7)
Children	G/A (0.19)	1.44 (1.25-1.66)	3.43E-07	32	.194	6651 (6)
Children	C/T (0.98)	0.44 (0.32-0.61)	3.49E-07	35	.174	9405 (6)
Children	T/G (0.05)	0.52 (0.41-0.67)	3.92E-07	20	.279	8627 (6)
Children	C/A (0.06)	1.59 (1.33-1.91)	4.02E-07	0	.837	12,883 (9)
Children	A/T (0.47)	0.7 (0.61-0.8)	4.16E-07	29	.208	5571 (7)
Children	A/G (0.2)	1.37 (1.21-1.55)	4.57E-07	12	.339	10,544 (8)
Adults	T/A (0.03)	1.92 (1.49-2.47)	5.00E-07	0	.792	226,600 (3)
Children	A/T (0.09)	1.5 (1.28-1.76)	5.57E-07	0	.757	7745 (8)
Adults	C/A (0.02)	2.41 (1.71-3.4)	5.92E-07	0	.984	226,480 (3)
Children	C/A (0.03)	2.04 (1.54-2.7)	6.60E-07	0	.606	9314 (6)
Adults	G/C (0.03)	1.46 (1.26-1.7)	6.74E-07	20	.274	34,378 (7)
Adults	A/G (0.05)	2.91 (1.91-4.44)	6.84E-07	0	.497	3021 (3)
Adults	T/C (0.09)	1.21 (1.12-1.31)	7.02E-07	42	.080	38,307 (10)
Adults	A/T (0.16)	1.9 (1.47-2.44)	7.43E-07	14	.326	3717 (5)
Adults	G/A (0.23)	0.78 (0.71-0.86)	7.90E-07	0	.916	229,426 (7)
Children	C/T (0.04)	1.85 (1.45-2.36)	8.15E-07	0	.950	7201 (6)
Children	A/G (0.2)	1.33 (1.19-1.49)	8.23E-07	25	.233	10,544 (8)
Adults	C/G (0.03)	1.43 (1.24-1.64)	8.47E-07	11	.347	37,326 (9)
Adults	A/G (0.06)	1.53 (1.29-1.81)	8.52E-07	0	.969	229,296 (6)
Adults	T/C (0.36)	1.12 (1.07-1.18)	8.63E-07	0	.930	39,864 (12)
Children	G/C (0.15)	1.56 (1.31-1.86)	9.07E-07	0	.698	5571 (7)
Adults	A/G (0.04)	2.14 (1.58-2.9)	9.75E-07	15	.316	3983 (4)

0.86, which is close to the loss-of-function intolerance threshold of 0.9.[37] 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 FA 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 doctor-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 doctor-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.[38,39] Heterogeneity of effects was observed between the pediatric and adult cohorts. 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.[40] This gene encodes a member of the fibrinogen family and is involved in processes of the immune system by suppressing T-cell mediation.[40] *FGL1*-knockout mice have been observed to develop spontaneous dermatitis and autoimmune diseases.[40] One of the candidate genes at the second locus, *NPAS3,*

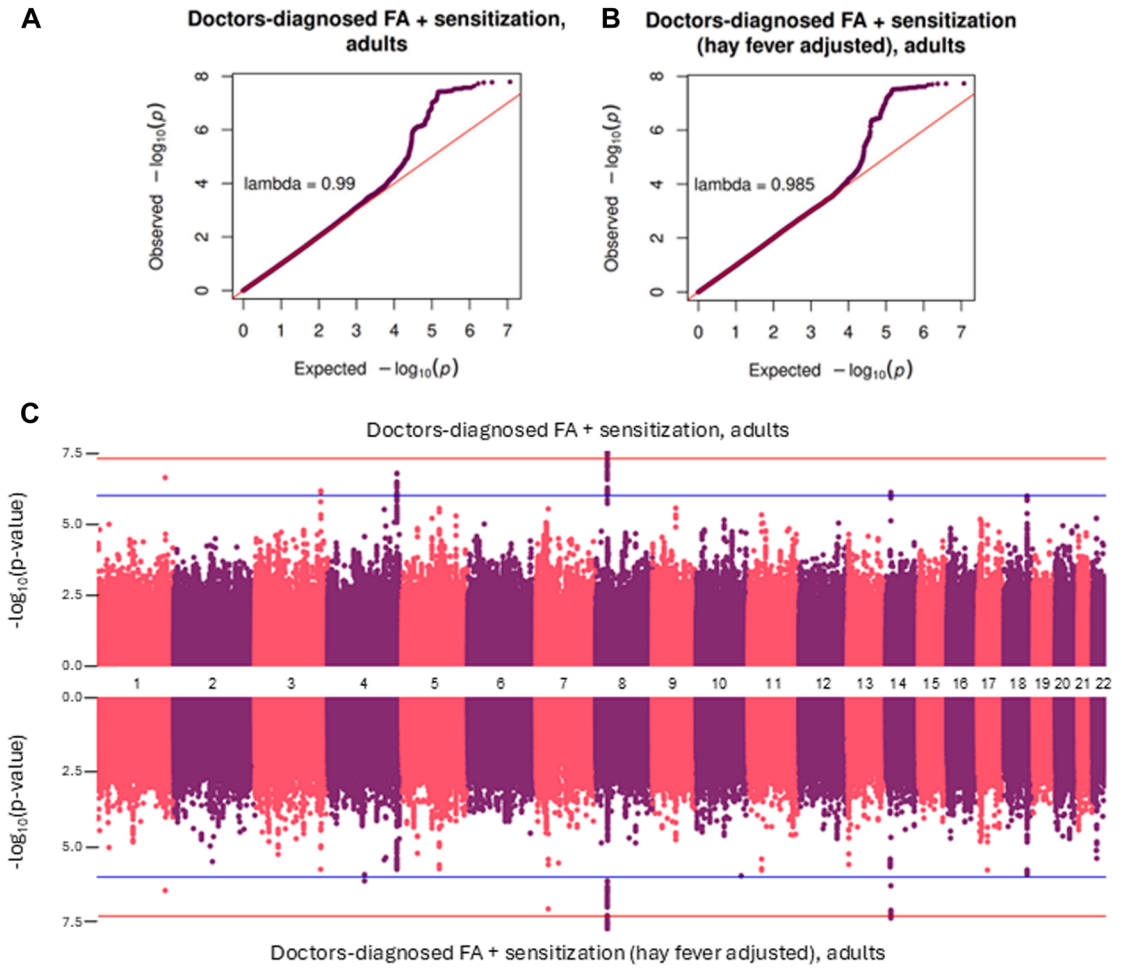

FIG 3. QQ plots for doctor-diagnosed FA plus food-specific sensitization in adults based on results from **(A)** main model and **(B)** hay fever–adjusted model. **(C)** Miami plots of meta-analyses for doctor-diagnosed FA plus food-specific sensitization in adults. Mirrored plots display baseline model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

had been linked to asthma in populations of European and African ancestry,[41] and both *AKAP6* and *NPAS3* have been reported to potentially play a role in metabolic syndrome.[42] 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 at allergy onset, reinforcing previous observations of shared genetic architecture across allergic conditions.[30-34] *KCNIP4, CASP4,* and *CASP5,* which were associated with doctor-diagnosed FA plus food-specific sensitization, are also known to play roles in allergic airway inflammation and the pathophysiology of asthma.[43,44] These genes further support the concept of a shared genetic background among atopic diseases and their underlying immunologic pathways, and they were all captured by analyses that used 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 because it may more reliably reflect heritability. This assumption was 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: $h^2 = 0.4\%$; 95% CI, −4.7, 5.6; children: $h^2 = 2.4\%$; 95% CI, −9.2, 13.9). In contrast, the more stringently defined phenotypes incorporating food-specific sensitization showed substantial SNP-based heritability ($h^2 = 34.0\%$; 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 the 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

TABLE II. 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*	Doctor-diagnosed FA	Main	Adults	G/A (0.3)	Asthma, atopic diseases, age at 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; *EAF,* EA frequency; *NEA,* non-EA.

self-reported FA does not differentiate primary FA from secondary FA (pollen-FA syndrome). 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 as a result of large standard errors and should be interpreted with caution.

This distinction is crucial for genetic studies because these conditions are clinically and genetically distinct.[17] In addition, another potential explanation is that a patient can be sensitized (ie, can have 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 the reduced local bioavailability of cysteinyl leukotrienes and the presence of disproportionating enzyme 1 (aka DPEP1) activity,[45,46] suggesting that barrier/epithelial–mast cell cross talk is a key determinant of clinical reactivity on 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 pediatric 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 at 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 doctor-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 as a result of limited sample size or phenotype misclassification. These findings suggest that there is 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,[7] of which 8 were nominally associated in children and 6 in adults in this study ($P < .05$). 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.[7] The nominally associated SNPs were mostly located in the *HLA* region, highlighting the critical role of immunologic mechanisms in general FA. Our study also confirmed that FA shares genetic risk factors with other allergic diseases.[30-34] Of 472 SNPs associated with allergic conditions, 229 loci were also associated with at least one FA phenotype ($P < .05$)—for example, *FLG* (see Table E28 in the Online Repository available at www.jacionline.org). 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. To our knowledge, 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. First, 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 and age as well as the heterogeneity of 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 to 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 at 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 FA phenotypes without such imputation may have diluted locus-specific signals, making it difficult to detect associations in this highly relevant region. Finally, a

TABLE III. Association results from discovery and replication stage in children

						Discovery
Variant	**Chr:position**	**Gene**	**Trait**	**Model**	**EA/NEA (EAF)**	**OR (95% CI)**
rs74991536	1:231163221	FAM89A	Doctor-diagnosed FA	Main, hay fever	C/T (0.98)	0.44 (0.32-0.61)
rs10899967‡	10:44509338	LINC00841, AL512640.1	Doctor-diagnosed FA	Main	A/G (0.2)	1.33 (1.19-1.49)
rs7108444	11:104857234	CASP4, CASP5	Doctor-diagnosed FA + sensitization	Main	G/C (0.15)	1.56 (1.31-1.86)
rs11645276	16:53092980	CHD9	Doctor-diagnosed FA + sensitization	Main	C/T (0.4)	0.68 (0.59-0.79)
rs11643761	16:9065990	RP11-77H9.8, RP11-473I1.6	Sensitization	Main	A/T (0.09)	1.5 (1.28-1.76)
rs4025780	17:764038	NXN	Doctor-diagnosed FA	Main	A/G (0.2)	1.37 (1.21-1.55)
rs16952200	18:7602849	PTPRM	Doctor-diagnosed FA	Hay fever	C/A (0.03)	2.04 (1.54-2.7)
rs1022311	2:180555884	ZNF385B	Doctor-diagnosed FA	Main, hay fever	T/C (0.1)	1.48 (1.28-1.72)
rs74531285	2:197132359	HECW2	Doctor-diagnosed FA	Main	T/C (0.02)	2.42 (1.75-3.36)
rs76119799	2:212415241	ERBB4	Self-reported FA	Main, hay fever	T/G (0.05)	0.52 (0.41-0.67)
rs78609709	2:53770433	GPR75-ASB3	Doctor-diagnosed FA + sensitization	Hay fever	C/A (0.04)	2.4 (1.73-3.32)
rs73174808	3:177288324	LINC00578	Self-reported FA	Main	C/A (0.06)	1.59 (1.33-1.91)
rs79989571	3:53474278	SNORA26, RP11-72H11.1	Self-reported FA	Hay fever	C/T (0.04)	1.85 (1.45-2.36)
rs62248296	3:68324177	FAM19A1	Self-reported FA	Hay fever	G/A (0.19)	1.44 (1.25-1.66)
rs2055684	3:69108316	UBA3	Doctor-diagnosed FA + sensitization	Main, hay fever	A/T (0.47)	0.7 (0.61-0.8)
rs6833463	4:21244175	KCNIP4	Doctor-diagnosed FA + sensitization	Main	A/G (0.24)	1.5 (1.3-1.74)
rs55681581	5:126981185	PRRC1, CTXN3	Self-reported FA	Main	T/C (0.15)	1.37 (1.22-1.55)

Alleles are reported as EA/other allele. Genome build, GRCh37/hg19. *EA,* Effect allele; *EAF,* EA frequency; *NEA,* non-EA.
*Studies included GENEVA and CLARA&CLAUS.
†Studies included GENEVA, GOFA, MAAS, and HealthNuts.
‡The following proxy was used in HealthNuts: rs10899968.

TABLE IV. Association results from discovery and replication stage in adults

Variant	**Chr:position**	**Gene**	**Trait**	**Model**	**EA/NEA (EAF)**
rs16849773	1:202204213	*LGR6*	Sensitization	Main	A/G (0.02)
rs117319649	10:47668777	*ANTXRL*	Sensitization	Main, hay fever	T/G (0.04)
rs56296494	10:5918344	*ANKRD16*	Sensitization	Main	A/G (0.04)
rs73228469	12:97466262	*RP11-541G9.1*	Doctor-diagnosed FA	Main	A/G (0.06)
rs138021736	13:50028384	*SETDB2*	Doctor-diagnosed FA	Main	T/A (0.03)
rs8022829	14:33397346	*AKAP6, NPAS3*	Doctor-diagnosed FA + sensitization	Main, hay fever	A/G (0.09)
rs61648937	15:41407730	*INO80*	Self-reported FA	Main	T/C (0.09)
rs12450646	17:5907793	*WSCD1*	Self-reported FA	Main	T/C (0.36)
rs2692192	3:180026087	*GAPDHP36, RP11-420J11.1*	Doctor-diagnosed FA + sensitization	Main	A/G (0.05)
rs72705776	4:180911393	*RP11-774G5.1, RP11-751A18.1*	Doctor-diagnosed FA + sensitization	Main	T/C (0.09)
rs62305340	4:84493126	*AGPAT9*	Doctor-diagnosed FA	Main	G/A (0.23)
rs12650891	4:94788391	*ATOH1, RP11-363G15.2*	Doctor-diagnosed FA + sensitization	Hay fever	A/T (0.16)
rs114560495	5:146894281	*DPYSL3, JAKMIP2*	Self-reported FA	Main, hay fever	G/C (0.03)
rs10265041	7:151127104	*RP4-555L14.4*	Self-reported FA	Main, hay fever	C/G (0.03)
rs11761070	7:24587280	*MPP6, RNU6-1103P*	Doctor-diagnosed FA + sensitization	Hay fever	C/A (0.07)
rs116936231	8:17753408	*FGL1*	Doctor-diagnosed FA + sensitization	Main, hay fever	T/C (0.02)
rs117937277	9:116941113	*COL27A1*	Doctor-diagnosed FA	Main	C/A (0.02)

Alleles are reported as EA/other allele. Genome build, GRCh37/hg19. *EA,* Effect allele; *EAF,* EA frequency; *NEA,* non-EA.
*Studies included UK Biobank.
†Studies included EXCEED.

Discovery		Replication in food-specific sensitization phenotype*			Replication in OFC phenotype†		
P	No. participants (no. studies)	OR (95% CI)	*P*	No. participants (no. studies)	OR (95% CI)	*P*	No. participants (no. studies)
3.49E-07	9405 (6)	1.05 (0.88-1.25)	.607	944 (2)	0.71 (0.48-1.05)	.092	5403 (3)
8.23E-07	10,544 (8)	1.05 (0.98-1.13)	.190	944 (2)	1.07 (0.93-1.24)	.343	5850 (4)
9.07E-07	5571 (7)	1.00 (0.92-1.09)	.996	492 (1)	0.93 (0.75-1.16)	.539	4992 (2)
3.07E-07	5571 (7)	1.00 (0.94-1.08)	.921	492 (1)	0.95 (0.81-1.12)	.555	4992 (2)
5.57E-07	7745 (8)	1.06 (0.96-1.18)	.252	492 (1)	1.06 (0.81-1.38)	.676	4992 (2)
4.57E-07	10,544 (8)	0.97 (0.9-1.05)	.404	492 (1)	1.1 (0.91-1.33)	.336	4992 (2)
6.60E-07	9314 (6)	1.01 (0.87-1.17)	.916	944 (2)	0.93 (0.65-1.33)	.694	4616 (2)
1.80E-07	10,544 (8)	0.98 (0.89-1.09)	.729	492 (1)	1.03 (0.81-1.30)	.779	5442 (3)
1.28E-07	8497 (5)	0.91 (0.71-1.18)	.489	492 (1)	1.29 (0.78-2.15)	.320	4992 (2)
3.92E-07	8627 (6)	1.06 (0.91-1.23)	.472	492 (1)	0.92 (0.62-1.37)	.682	4992 (2)
1.40E-07	5188 (6)	1.14 (0.99-1.3)	.064	944 (2)	1.01 (0.75-1.36)	.955	5403 (3)
4.02E-07	12,883 (9)	0.98 (0.85-1.12)	.717	492 (1)	0.83 (0.57-1.21)	.331	4992 (2)
8.15E-07	7201 (6)	1.02 (0.9-1.16)	.759	944 (2)	0.98 (0.72-1.33)	.887	5403 (3)
3.43E-07	6651 (6)	1.04 (0.95-1.14)	.366	492 (1)	0.85 (0.69-1.06)	.148	4992 (2)
4.16E-07	5571 (7)	1.02 (0.96-1.09)	.525	492 (1)	1.08 (0.94-1.24)	.273	5444 (3)
5.05E-08	5571 (7)	0.97 (0.85-1.12)	.689	943 (2)	1 (0.88-1.15)	.954	5854 (4)
2.74E-07	12,514 (9)	1.02 (0.94-1.1)	.689	492 (1)	0.87 (0.72-1.04)	.128	5428 (3)

Discovery			Replication in self-reported FA phenotype*			Replication in doctor-diagnosed FA phenotype†		
OR (95% CI)	*P*	No. participants (no. studies)	OR (95% CI)	*P*	No. participants (no. studies)	OR (95% CI)	*P*	No. participants (no. studies)
2.4 (1.72-3.34)	2.46E-07	3056 (3)	0.99 (0.99-1.00)	.44	361,141 (1)	2.38 (1.14-4.99)	.02	7062 (1)
2.52 (1.79-3.57)	1.58E-07	3247 (3)	NA	NA	NA	NA	NA	NA
2.14 (1.58-2.9)	9.75E-07	3983 (4)	1.00 (0.99-1.00)	.62	361,141 (1)	1.11 (0.47-2.61)	.81	7062 (1)
1.53 (1.29-1.81)	8.52E-07	229,296 (6)	0.99 (0.99-1.00)	.38	361,141 (1)	1.4 (0.7-2.82)	.34	7062 (1)
1.92 (1.49-2.47)	5.00E-07	226,600 (3)	0.99 (0.99-1.00)	.53	361,141 (1)	1.76 (0.75-4.09)	.19	7062 (1)
1.99 (1.52-2.62)	7.74E-07	4050 (5)	1.00 (0.99-1.00)	.07	361,141 (1)	0.72 (0.42-1.23)	.23	7062 (1)
1.21 (1.12-1.31)	7.02E-07	38,307 (10)	0.99 (0.99-1.00)	.69	361,141 (1)	0.95 (0.58-1.56)	.84	7062 (1)
1.12 (1.07-1.18)	8.63E-07	39,864 (12)	1.00 (0.99-1.00)	.79	361,141 (1)	1.08 (0.79-1.49)	.62	7062 (1)
2.91 (1.91-4.44)	6.84E-07	3021 (3)	1.00 (0.99-1.00)	.21	361,141 (1)	1.21 (0.61-2.4)	.59	7062 (1)
2.13 (1.61-2.83)	1.66E-07	4050 (5)	0.99 (0.99-1.00)	.41	361,141 (1)	1.17 (0.69-1.99)	.56	7062 (1)
0.78 (0.71-0.86)	7.90E-07	229,426 (7)	1.00 (0.99-1.00)	.50	361,141 (1)	0.83 (0.57-1.2)	.32	7062 (1)
1.9 (1.47-2.44)	7.43E-07	3717 (5)	1.00 (0.99-1.00)	.68	361,141 (1)	1.2 (0.79-1.83)	.40	7062 (1)
1.46 (1.26-1.7)	6.74E-07	34,378 (7)	1.00 (0.99-1.00)	.99	361,141 (1)	1.16 (0.48-2.8)	.74	7062 (1)
1.43 (1.24-1.64)	8.47E-07	37,326 (9)	1.00 (0.99-1.00)	.24	361,141 (1)	1.33 (0.58-3.03)	.50	7062 (1)
2.89 (1.96-4.26)	8.70E-08	3031 (3)	1.00 (1-1.00)	.05	361,141 (1)	0.65 (0.35-1.23)	.18	7062 (1)
4.76 (2.77-8.18)	1.62E-08	3047 (3)	0.99 (0.99-1.00)	.14	361,141 (1)	0.44 (0.13-1.44)	.17	7062 (1)
2.41 (1.71-3.4)	5.92E-07	226,480 (3)	0.99 (0.99-1.00)	.76	361,141 (1)	0.48 (0.18-1.26)	.14	7062 (1)

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, which to our knowledge is the largest conducted to date on FA, identified 37 SNPs with suggestive associations, highlighting genetic distinctions between FA in childhood and adulthood as well as across phenotypes and age groups; it also identified genetic factors shared 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 the power to identify genetic associations with atopic diseases, the inherent heterogeneity of FA necessitates collaborative efforts to refine research approaches while also permitting investigation of specific food allergens. In addition, creating a polygenic risk score to sum up the many small effects of many variants into a single risk metric may provide additional insights.

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Key messages

- **This GWAS meta-analyses on FA comprising 229,426 adults and 14,234 children identified 37 suggestive SNPs, with 2 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 indicating that doctor-diagnosed FA provides the most reliable phenotype for future analyses.**

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