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Evaluation of food allergy candidate loci in the Genetics of Food Allergy study



To the Editor:

Food allergy (FA) is a common health problem with a strong genetic etiology. Twin studies estimated FA heritability at about 80%,^{1,2} but our knowledge of the genes underlying FA is still sparse. A recent genome-wide association study (GWAS) on FA published in the *Journal of Allergy and Clinical Immunology* investigated 850 cases from the Canadian Peanut Allergy Registry (CanPAR) and 926 Australian controls.³ The CanPAR study successfully identified a new FA locus on chromosome 11q13, near the genes *C11orf30* (chromosome 11 open reading frame 30) and *LRRC32* (leucine-rich repeat-containing 32), and proposed additional risk variants for further investigation that did not meet the threshold of genome-wide significance.³

Here, we aimed to evaluate the findings of the CanPAR study in an independent study population, the German Genetics of Food Allergy (GOFA) study. The GOFA study consists of 902 cases with FA, including 342 with peanut allergy, and 3668 control individuals of unknown phenotype from 2 German population-based studies, the Heinz Nixdorf Recall Study (n = 2682) and the Study of Health in Pomerania (n = 986). A GWAS on the GOFA study has recently been published and identified 5 genome-wide significant susceptibility loci for FA and peanut allergy.⁴ Most GOFA study cases were diagnosed by

TABLE I. Characterization of the GOFA study

Characteristic	GOFA study
Total number of samples	902
Sex	64% males
Age (y), mean $\pm$ SD*	4.8 $\pm$ 3.6
Diagnosis, n (%)	
Double-blind, placebo-controlled food challenge	650 (72)
Oral food challenge	125 (14)
Severe allergic reaction plus elevated allergen-specific serum IgE (>0.35 kU/L)	127 (14)
Food allergies, n (%)	
Hen's egg	504 (56)
Peanut	352 (39)
Cow's milk	276 (31)

*Mean age at last visit.

double-blind, placebo-controlled food challenges (Table I), the current gold standard for the diagnosis of FA.^{5,6} Detailed information on clinical phenotypes, study population, genotyping, and statistical analyses is provided in this article's **Methods** section in the Online Repository at www.jacionline.org. After quality control, 866 cases including 336 peanut-allergic children and 3358 controls were included in our case-control association study on FA.

In line with the CanPAR study,³ we have previously reported genome-wide significant association of the *C11orf30/LRRC32* locus with FA.⁴ Analyzing the CanPAR lead single nucleotide polymorphism (SNP), rs7936434, in the GOFA study revealed association with FA ($P = 1.6 \times 10^{-7}$) and with peanut allergy ($P = .0024$; Table II), which was significant after correction for the number of markers tested. Since rs7936434 is in high linkage disequilibrium (LD) with the previously reported, best-associated SNP of the GOFA study, rs2212434 ($r^2 = 0.89$), both variants represent the same locus. In addition, we investigated the other 7 independent SNPs, rs115218289, rs72827854, rs144897250, rs7475217, rs744597, rs523865, and rs78048444, which were suggestive of association with FA in the CanPAR GWAS. Two additional variants reported in that study (rs56151068 and rs139462954) were in very high LD with the lead variant rs72827854 ($r^2 > 0.92$) on chromosome 17, thus representing the same association. All candidate SNPs were either genotyped or imputed with high quality ($r^2 > 0.75$) in the GOFA study. None of the 7 candidate SNPs was associated with FA in our study (Table II). Because all CanPAR cases were recruited through peanut allergy, we then tested whether the reported associations were peanut-specific. However, restricting the analysis to the subset of peanut-allergic children from the GOFA study did not change the results (Table II). We used the Genetic Power calculator⁷ to assess the power of our study sample for replication. Based on the allele frequencies and the reported effect sizes, the GOFA study provided nearly 100% power to detect association of the candidate variants with FA at the Bonferroni-corrected significance threshold of $P < .00714$. The power to detect a peanut-specific effect was reduced for only 2 low-frequency variants (rs115218289 and rs78048444) but still exceeded 80% for a nominal significance level (see Table E1 in this article's Online Repository at www.jacionline.org).

In the CanPAR study, 7 loci suggestive for association with FA were reported, which were not confirmed in independent study populations included in the original report.³ Because

TABLE II. The GOFA study association results of the SNPs reported in the CanPAR GWAS

Table 1. The GOFA study association results of the SNPs reported in the CanPAR study													

Chr, Chromosome; MAF, minor allele frequency; OR, odds ratio.

*Minor/major allele.

†As compared with the risk allele in the CanPAR study.

‡Only rs7936434 reached genome-wide significance in the CanPAR meta-analysis after including independent study populations.

nonreplication is not necessarily due to false-positive results in the discovery study, we evaluated these 7 candidate loci in the GOFA study and did not verify the CanPAR study results. One potential cause of nonreplication is lack of power due to small study size. This is unlikely to be the case in the GOFA study because power calculations demonstrated that our study sample had excellent power to replicate the reported genetic effects in FA. Even in the subanalysis of low-frequency variants in peanut allergy, our sample was sufficiently powered to detect effects at nominal significance.

Another obstacle to the genetic investigation of FA is the difficulty in obtaining a reliable diagnosis. It is well recognized that the prevalence of FA is grossly overestimated if based on patients' history of an adverse reaction to food.⁵ Even if the results of allergy tests were taken into account, the prevalence of FA was overestimated by a factor of 3 compared with challenge-proven FA. Thus, current medical guidelines recommend standardized oral food challenges as the gold standard to diagnose FA,^{5,6} which are, however, demanding and expensive to perform. The strength of the GOFA study lies in its large sample size in combination with a well-defined FA phenotype that was based on oral food challenges.

Differences between the CanPAR study and the GOFA study results might be further explained by different inclusion criteria used for the 2 studies. For the CanPAR study, all patients were recruited through peanut allergy, whereas the GOFA study also investigated patients with allergic responses against other food allergens such as hen's egg and cow's milk. Interestingly, the only allergen-specific locus identified so far, the HLA locus for peanut allergy,⁸ was also identified at genome-wide significance in peanut-allergic children of the GOFA study, highlighting the power of this study to identify allergen-specific associations.

Another source of variation may originate from the use of different genotyping arrays. The CanPAR GWAS used the same genotyping array for cases and controls, whereas in the GOFA study, cases and controls were genotyped on different Illumina arrays. However, for genotype imputation, only markers genotyped on both arrays were used, which is state-of-the-art.⁹ In addition, we applied stringent quality control to ensure high data quality as confirmed by a genomic inflation factor lambda of 1.03 for FA and peanut allergy.⁴

Finally, confounding environmental factors and population-specific genetic characteristics might hamper the replication of disease-associated SNPs. Both studies, the CanPAR study and the GOFA study, investigated study populations of Caucasian ethnic origin, which is reflected in very similar marker allele frequencies (Table II). Likewise, differences in LD patterns, which may be observed if populations of diverse ethnic origin are being compared, should be minor between the 2 studies.

Problems may particularly arise from population admixture and population stratification, which may yield false-positive association results if not strictly controlled for. Accordingly, all GOFA study cases and controls originated from Germany and were ethnically homogeneous, as confirmed by STRUCTURE. A lambda close to 1 pointed to the absence of population structure in our data set.

In summary, evaluation of the CanPAR study lead variant on chromosome 11q13 in the GOFA study revealed that both studies identified the same FA locus. We found no evidence supporting the association of the 7 candidate loci reported in the CanPAR GWAS. Combined efforts to achieve larger sample sizes with well-defined, standardized phenotypes and the integration of other genomic resources, including gene expression/regulation data, will be required to identify novel genetic associations with FA.

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Calcium and zinc tune autoinflammatory Toll-like receptor 4 signaling by S100A12



To the Editor:

Autoinflammatory diseases (AIDs) are characterized by recurrent episodes of systemic inflammation in absence of infection or

autoimmunity.¹ The granulocytic protein S100A12 as well as closely related myeloid-related S100A8/A9 are highly overexpressed in some of these disorders and their serum titers can indicate disease flares or response to therapy.^{E1-E3} As reason for their value as biomarkers it is thought that these proteins by themselves induce sterile inflammation.^{2,E4,E5} This can be triggered by damage-associated molecular patterns (DAMPs, “alarmins”), which are recognized by innate immune cells via sensors such as Toll-like receptor 4 (TLR4).³ S100A8/A9 and S100A12 can operate as DAMPs, yet clarifying their TLR4-interaction mode may provide better understanding of their role in AID pathology.^{2,4,E6,E7}

In this context, it is remarkable that the S100A12 structure is significantly impacted by Ca²⁺ binding and Zn²⁺ binding.⁵ In AIDs, Zn²⁺ serum and plasma levels are reported to remain at or in part massively exceed healthy control levels, which is in contrast to inflammation resulting from infection.^{6,E8,E9} We therefore aimed to investigate the relevance of Zn²⁺ and Ca²⁺ in tuning the TLR4-dependent DAMP function of S100A12 in autoinflammation.

Initially, we observed S100A12 to strongly bind human TLR4 (hTLR4)/myeloid differentiation protein-2 (MD2) when in buffers containing Zn²⁺, regardless of whether S100A12 was sensor-chip immobilized in buffer spiked with just Ca²⁺ (Fig 1, A) or both Ca²⁺ and Zn²⁺ (Fig 1, B). Latter conditions rendered S100A12 a high-affinity TLR4 ligand ($K_D = 0.2 \pm 0.06$ nM; Fig 1, C). Only buffer or just Ca²⁺ established no S100A12 binding to TLR4/MD2. Similarly, addition of the Zn²⁺>Ca²⁺-chelator EDTA abrogated S100A12 binding to TLR4/MD2 (Fig 1, A and B).

Next, on the basis of amino acid sequence of ion-binding incapable S100A10 (Fig 1, D), we substituted one Zn²⁺-coordinating residue (D25; Fig 1, E) or residues constituting the protein's primary Ca²⁺-binding site by alanine (N63E72; Fig 1, F). In kinetic stimulation experiments of primary human monocytes with these mutants, we observed strong reduction of the proinflammatory as well as IFN- β -related cyto-/chemokine secretion profile compared with LPS-free wild-type S100A12 or LPS stimulations (Fig 1, G and H; see Fig E1, A and B, in this article's Online Repository at www.jacionline.org). Because recently Ca²⁺ binding to S100A12 has been demonstrated to tune the protein's Zn²⁺ chelating,⁷ our monocyte stimulation and surface plasmon resonance data collectively suggest disturbed Zn²⁺ sequestering to impair both TLR4 binding and signaling by S100A12. Importantly, we observed both mutants to impair Ca²⁺- and Zn²⁺-induced oligomerization into defined tetrameric and hexameric quaternary structures as observed with wild-type S100A12 (Fig 1, I).

Furthermore, we generated defined S100A12 oligomers fixed by chemical crosslinking and separated by size exclusion chromatography (Fig E1, C and D). In stimulation experiments using hTLR4/CD14/MD2-expressing 293 cells (Fig 1, J) as well as primary human monocytes (Fig 1, K and L; Fig E2, A, B and D), only hexameric S100A12 was able to induce *IL8* reporter gene (Fig 1, J), monocytic TNF- α release (Fig 1, K and L), or gene (see Fig E2, A and B, in this article's Online Repository at www.jacionline.org) expression, respectively. Although qualitative TLR4/MD2-binding data suggest some binding of tetrameric S100A12 (Fig E2, C), neither dimeric nor tetrameric protein reduced hexamer-induced monocytic TNF- α release (Fig E2, D). However, TNF- α expression was efficiently impaired by

METHODS

Clinical phenotypes

According to the current guidelines, FA was diagnosed on the basis of oral food challenges (OFCs; $n = 775$ [86%]), most of which ($n = 650$) were conducted in a double-blind placebo-controlled setting. Children with a convincing history of an immediate, severe allergic reaction plus specific sensitization to the same food ($\text{IgE} > 0.35 \text{ kU/L}$) were included as cases without further challenge ($n = 127$), because OFC is contraindicated because of the risk of severe anaphylactic reactions.

OFCs were performed in an inpatient hospital setting under physicians' supervision. Only 1 food or placebo was investigated per 24-hour period and was administered in 7 escalating doses at 30-minute intervals. Consistent with PRACTALL guidelines, food challenges were scored as positive if objective cutaneous, gastrointestinal, respiratory, or cardiovascular reactions attributable to the allergen, but not to placebo, were observed.^{E1}

Study population

Children of the GOFA study were recruited at clinical centers in Berlin, Wangen, Hannover, and Oldenburg, Germany. The study population combines set 1 and set 2 of the previous GWAS on FA.^{E2} In total, 902 food-allergic children were recruited for the GOFA study. Clinical characteristics are described in detail in Table I. Control individuals without information on FA were derived from the Heinz Nixdorf Recall Study ($n = 2682$), a population-based cohort study for cardiovascular disease^{E3} comprising 4800 randomly selected individuals from Ruhr area in Germany. Additional samples were available from the Study of Health in Pomerania ($n = 986$), which is a population-based cohort from North-Eastern Germany.^{E4} Our study was approved by the local ethics committees, and written informed consent was given by all participants or their legal guardians.

Genotyping and imputation

Samples were genotyped on Illumina's HumanOmniExpressExome-8 v1.2, HumanOmniExpress-12 v1.0, or HumanOmni1-Quad v1 arrays. Quality control criteria were the same as described previously.^{E2} In addition, ethnic homogeneity was confirmed using the software STRUCTURE.^{E5} After quality control, the study population included 866 cases with FA of which 336 were allergic to peanut and 3358 controls. Genotype imputation was performed on the Michigan Imputation Server (<https://imputationserver.sph.umich.edu/index.html>)^{E6} using the Haplotype Reference Consortium (version r1.1) panel.^{E7} Because genotyping was performed on different Illumina SNP arrays, we used only those SNPs for imputation that were genotyped on all arrays.^{E8} For phasing, SHAPEIT v2 was used,^{E9} and imputation was done with minimac3.^{E6} After imputation, we excluded SNPs with poor imputation quality ($r^2 < 0.5$) and deviation from HWE ($P < 10^{-12}$ in controls).

Statistical analyses

The association study was performed in 866 cases with FA and 3358 control individuals. For peanut allergy, 336 cases and 3358 controls were analyzed.

Association between the candidate variants and disease was analyzed with PLINK^{E10} using logistic regression and including sex as covariate. P values of less than .00714 were regarded as statistically significant.

Power calculations

We tested 7 independent variants for association with FA and performed a power calculation for each of the variants.^{E11} To estimate the power of our study for detecting the reported SNP associations, we used an allelic model with 5% disease prevalence and $\alpha = 0.00714$ ($=0.05/7$). For each SNP, we used the allele frequency identified in our study population (which was in line with the CanPAR study) and the effect size reported in the CanPAR GWAS (Table E1).

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TABLE E1. Power calculation for the candidate SNPs

SNP ID	MAF	OR	Power*			
			FA (n = 866) P = .00714	FA (n = 866) P = .05	PNA (n = 338) P = .00714	PNA (n = 338) P = .05
Rs115218289	0.026	0.18	1	1	0.77	0.93
rs744597	0.425	0.61	1	1	1	1
rs78048444	0.024	0.22	0.98	1	0.67	0.88
rs7475217	0.415	1.64	1	1	1	1
rs144897250	0.016	6.20	1	1	1	1
rs72827854	0.107	2.16	1	1	1	1
rs523865	0.230	0.57	1	1	0.99	1

MAF, Minor allele frequency; OR, odds ratio; PNA, peanut allergy.

*Parameters used for power calculation were alpha, 0.00714 and 0.05, respectively; prevalence, 0.05; unselected controls, n = 3358.