Genome-wide association study and admixture mapping reveal new loci associated with total IgE levels in Latinos

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Background: IgE is a key mediator of allergic inflammation, and its levels are frequently increased in patients with allergic disorders.
Objective: We sought to identify genetic variants associated with IgE levels in Latinos.
Methods: We performed a genome-wide association study and admixture mapping of total IgE levels in 3334 Latinos from the Genes-environments & Admixture in Latino Americans (GALA II) study. Replication was evaluated in 454 Latinos, 1564 European Americans, and 3187 African Americans from independent studies.
Results: We confirmed associations of 6 genes identified by means of previous genome-wide association studies and identified a novel genome-wide significant association of a polymorphism in the zinc finger protein 365 gene *(ZNF365)* with total IgE levels (rs200076616, $P = 2.3 \times 10^{-8}$). We next identified 4 admixture mapping peaks (6p21.32-p22.1, 13p22-31, 14q23.2, and 22q13.1) at which local African, European, and/or Native American ancestry was significantly associated with IgE levels. The most significant peak was 6p21.32-p22.1, where Native American ancestry was associated with lower IgE levels ($P = 4.95 \times 10^{-8}$). All but 22q13.1 were replicated in an independent sample of Latinos, and 2 of the peaks were replicated in African Americans (6p21.32-p22.1 and 14q23.2). Fine mapping of 6p21.32-p22.1 identified 6 genome-wide significant single nucleotide polymorphisms in Latinos, 2 of which replicated in European Americans. Another single nucleotide polymorphism was peak-wide significant within 14q23.2 in African Americans (rs1741099, $P = 3.7 \times 10^{-6}$) and replicated in non–African American samples ($P = .011$).
Conclusion: We confirmed genetic associations at 6 genes and identified novel associations within *ZNF365*, *HLA-DQA1*, and 14q23.2. Our results highlight the importance of studying diverse multiethnic populations to uncover novel loci associated with total IgE levels. (J Allergy Clin Immunol 2014;■■■:■■■-■■■.)

Key words: *IgE, genome-wide association study, admixture mapping, allergy, asthma, next-generation sequencing, Latinos, Hispanics, minority populations*

Abbreviations used

eQTL:	Expression quantitative trait locus
GALA I:	Genetics of Asthma in Latino Americans
GALA II:	Genes-environments & Admixture in Latino Americans
GPHB5:	Glycoprotein hormone beta 5
GRAAD:	Genetic Research on Asthma in the African Diaspora
GWAS:	Genome-wide association study
Indel:	Insertion-deletion
KCNH5:	Potassium voltage-gated channel, subfamily H (eag-related), member 5 gene
RHOJ:	Ras homolog family member J gene
SNP:	Single nucleotide polymorphism
ZNF365:	Zinc finger protein 365 gene

IgE is a class of antibody involved in host defense mechanisms against parasitic infections.[1,2] Increased total IgE levels are strongly associated with allergic disorders[1] and asthma severity.[3] Monoclonal antibodies against IgE have proved to be effective in decreasing asthma exacerbations and allergic inflammation,[4,5] highlighting the importance of IgE in the cause of both asthma and allergic disease.

The high heritability of IgE levels (47% to 80%),[6-8] the clinical and biological relationship of IgE with atopic diseases, and the ability to measure IgE levels in serum with a high precision make IgE a useful endophenotype for the study of atopic diseases.[1,9] Consequently, many linkage analyses and candidate gene association studies have identified genes associated with IgE levels.[9] Recently, 5 genome-wide association studies (GWASs) have revealed single nucleotide polymorphisms (SNPs) near 12 genes to be associated with IgE levels at a genome-wide significance level, including 6 genes within the major MHC.[10-13]

Only 1% of subjects within prior GWASs were Latinos,[10-14] and therefore studying diverse populations might uncover some

of the additional missing heritability of IgE levels.[15] This is particularly relevant for studies of IgE because it is known to vary by race-ethnicity in the United States, with higher levels reported in both Latinos and African Americans compared with European Americans.[16-19] Differences in IgE levels among ethnic groups might in part be due to variation in the frequencies of risk alleles for high IgE levels resulting from different proportions of Native American, European, and African genetic ancestry at an individual locus (local ancestry). Consistent with this, African ancestry has been associated with higher IgE levels in populations of African descent,[20,21] suggesting that admixture mapping could be a powerful tool to identify novel loci associated with IgE levels, as shown for other traits and diseases.[22-24] Therefore in this study we reasoned that novel genetic variants associated with IgE levels in Latinos could be identified through a combination of GWAS and admixture mapping.

METHODS

Study populations

Genes-environments & Admixture in Latino Americans (GALA II) study. A total of 3334 participants were used for discovery (see Table E1 in this article's Online Repository at www.jacionline.org). The GALA II study is an ongoing, multicenter

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case-control study of asthma in Latino children (Puerto Rican, Mexican, and other Latinos) recruited from the mainland United States and Puerto Rico and approved by all local institutional review boards. All participants/parents provided written assent/consent, respectively.

Total serum IgE levels were measured in duplicate on the ImmunoCAP 100 system (Phadia, Kalamazoo, Mich). Subjects were genotyped on the Axiom LAT1 array (World Array 4; Affymetrix, Santa Clara, Calif),[25] as described elsewhere.[23]

The Genetics of Asthma in Latino Americans (GALA I) study. Characteristics of the 454 asthma cases from the GALA I study used for replication are shown in Table E1. Subjects were recruited from the United States and Mexico City. Total IgE levels were measured, as described in the GALA II study, and genotyping was performed on the Affymetrix 6.0 GeneChip (Affymetrix).[22]

Additional replication studies. Further replication was performed in European and African American studies from the EVE Consortium with measured IgE levels (see Table E2 in this article's Online Repository at www.jacionline.org).[13,26] African American studies included the Study of Asthma Phenotypes and Pharmacogenomic Interactions by Race-ethnicity, the Genetic Research on Asthma in the African Diaspora in African American subjects (GRAAD-AA) and in Afro-Caribbean subjects from Barbados (GRAAD-AC), and the Chicago Asthma Genetics study, Collaborative Studies on the Genetics of Asthma, and the Severe Asthma Research Program (Chicago Asthma Genetics Study/Collaborative Studies of the Genetics of Asthma/Severe Asthma Research Program). European American studies with measured IgE levels included the Childhood Asthma Management Program, the Childhood Asthma Research and Education Network, and the Chicago Asthma Genetics Study/Collaborative Studies of the Genetics of Asthma/Severe Asthma Research Program.

Statistical analysis

GWASs. Quality control was performed by removing SNPs with genotyping call rates of less than 95% and/or that deviated from Hardy-Weinberg equilibrium ($P < 10^{-6}$) within control subjects. Samples with discrepancy between genetic sex and reported sex and with cryptic relatedness (proportion of identity by descent > 0.3) were also removed. Allelic association testing between genotypes at individual SNPs with natural log-transformed total serum IgE levels was performed assuming an additive model by using linear regression in R 2.14[27] and adjusting for age, sex, ethnicity, asthma status, and African and Native American global ancestries. We also evaluated a model adjusting for local African and Native American ancestry. Regions with more than 1 SNP associated with IgE levels at a P value of 5×10^{-6} or less underwent *in silico* fine mapping by using genotype imputation. For that, genotyped SNPs were phased with SHAPE-IT,[28] followed by imputation with IMPUTE2,[29] considering all populations from the 1000 Genomes Project Phase I v3 as a reference.[30] In addition, we evaluated whether SNPs associated with IgE levels were associated with related phenotypes (atopic dermatitis, asthma, rhinitis, and allergic sensitization) or showed an interaction with asthma status.

Admixture mapping. Estimates of local ancestry were obtained by using the software Local Ancestry in adMixed Populations using Linkage Disequilibrium (LAMP-LD) under a 3-population model[31] with reference haplotypes from the HapMap phase II CEU (European) and YRI (African) and 71 Native American subjects genotyped on the Axiom LAT1 array.[23] Inferred local ancestry was then used to perform admixture mapping by correlating levels of local African, European, and Native American ancestry across the genome with natural log-transformed IgE levels by using linear regression and adjusting for age, sex, ethnicity, global ancestry, and asthma status. To study whether overlapping peaks found for IgE levels and asthma were due to pleiotropic effects (ie, loci influencing IgE and asthma together) and not confounded by means of linkage disequilibrium, we used a Bayesian network method implemented in the package *bnlearn* for R.[32] See the Methods section in this article's Online Repository at www.jacionline.org for more details.

The effective number of ancestry blocks was estimated by using an empiric autoregression framework with the package *coda* for R to account for multiple testing. On the basis of the number of ancestry blocks in the GALA II study (1041), we established a Bonferroni P value threshold for significance as follows:

$$\alpha = 0.05/1041 = 4.8\times10^{-5},$$

which is similar to Shriner et al.[33] Statistically significant admixture mapping peaks were brought forth for replication in the GALA I study and the African American EVE Consortium studies by using linear regression models. A linear mixed-effects model was used for one study with extended pedigree structure (GRAAD-AC).[34] A meta-analysis was performed with METASOFT to assess the overall effect size of local ancestry across studies.[35]

Fine mapping of significant admixture mapping peaks was performed by using allelic association testing with both genotyped and imputed SNPs. A Bonferroni correction based on the number of genotyped SNPs within each peak was used to provide a peak-wide threshold of significance. Peak-wide significant SNPs identified in the GALA II study were brought for replication in the rest of studies. For Latinos and African Americans, we adjusted for global ancestry estimates, and for European Americans, we adjusted for 2 principal components from a principal component analysis.[26]

Functional annotation of associated SNPs. Functional annotation of associated SNPs and enhancer enrichment analysis was carried out with HaploReg.[36] Expression quantitative trait loci (eQTLs) were identified by querying the Geuvadis Data Browser.[37]

Exon sequencing. We sequenced the coding and untranslated region exons of 3 genes, including 1 gene identified through GWASs (the zinc finger protein 365 gene *[ZNF365]*) and 2 genes encoding human leukocyte antigens (HLA), identified through fine mapping of admixture mapping peaks (*HLA-DQB1* and *HLA-DRB5* within 6p21-22). All Puerto Ricans from the GALA II study included in the study were sequenced (n = 1454). Exons were targeted by using Molecular Inversion Probe technology, as described elsewhere.[38,39] Targeted regions were sequenced on a MiSeq sequencer (Illumina, San Diego, Calif) by using 150-bp reads. Output reads were aligned to the human genome (hg19) with the Burrows-Wheeler Aligner,[40] and variant calling was performed with the Genome Analysis Toolkit.[41,42] Variants were annotated by using SeattleSeq (http://snp.gs.washington.edu).

Association testing was performed by using linear regression models for individual variants with PLINK.[43] Given that single-variant tests might have reduced statistical power to detect an association with rare variants, we also analyzed the cumulative association of multiple rare variants with IgE levels by using the Sequence Kernel Association Test, as adjusted by the same covariates as for individual allelic association testing.[44] Sets of pooled nonsynonymous, synonymous, and noncoding variants were analyzed separately.

A flow chart with the study design is shown in Fig E1, and additional information is shown in the Methods section in this article's Online Repository at www.jacionline.org.

RESULTS

GWASs

Manhattan plots of GWAS results for unadjusted models versus models adjusted by local genetic ancestry are shown in Figs E2, *A* and *B*, in this article's Online Repository at www.jacionline.org, respectively. The quantile-quantile plot for an unadjusted model (see Figs E2, *C*) showed higher but still minimal genomic inflation ($\lambda_{GC} = 1.05$) than seen in the model adjusted for local ancestry ($\lambda_{GC} = 1.02$; Figs E2, *D*). Several SNPs within a 50-kb window at 10p21.2 had a P value of 5×10^{-6} or less in the model adjusted by local ancestry (see Table E3 in this article's Online Repository at www.jacionline.org). Fine mapping of this region by imputing variants from the 1000 Genomes Project revealed a common insertion-deletion (indel) in *ZNF365* that reached genome-wide significance (rs200076616, $\beta = -0.23$ for the insertion allele, $P = 2.3 \times 10^{-8}$; Fig 1). This indel was

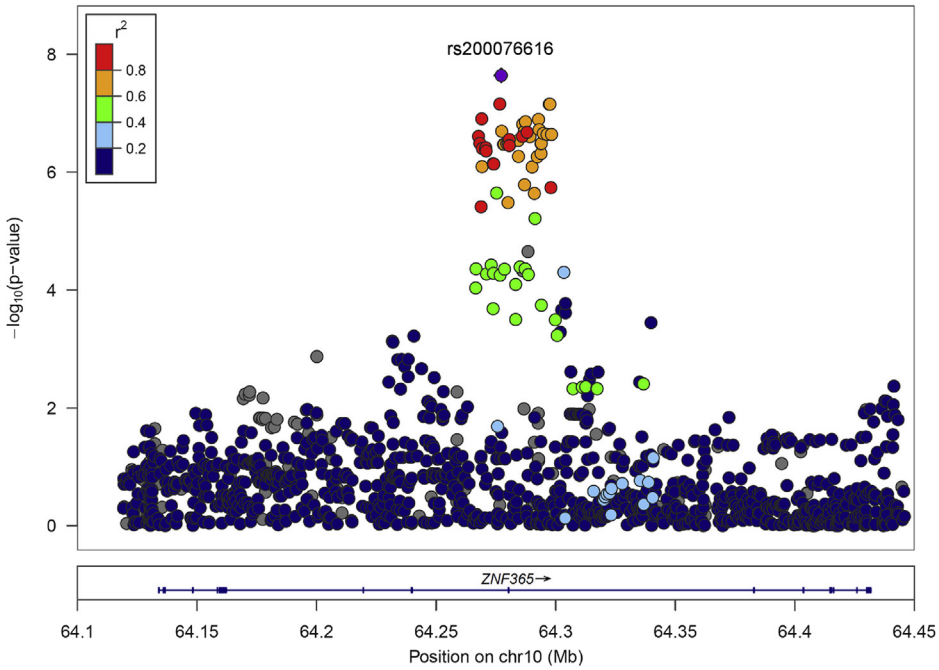

FIG 1. Fine mapping of *ZNF365* in the GALA II study. Included in the plot are $-\log_{10}(P$ values) of association with total serum IgE levels by chromosome position. The most significant SNP is represented by a *diamond*, and the results for the remaining SNPs are color coded to show their linkage disequilibrium with this SNP based on pairwise r^2 values from the Latino populations of the 1000 Genomes Project. SNPs above the dashed line are genome-wide significant ($P \leq 5 \times 10^{-8}$).

significantly associated with IgE levels in all 3 subgroups of Latinos from the GALA II study: Mexicans ($\beta = -0.25$, $P = 9.2 \times 10^{-5}$), Puerto Ricans ($\beta = -0.21$, $P = 8.4 \times 10^{-4}$), and other Latinos ($\beta = -0.21$, $P = .020$). However, the association was in the opposite direction in the GALA I study ($\beta = 0.22$, $P = .038$) and did not replicate in African Americans and European Americans from the EVE Consortium studies ($\beta = -0.07$, $P = .090$ and $\beta = -0.06$, $P = .281$, respectively). A summary of SNPs with a P value of 5×10^{-6} or less in models unadjusted by local ancestry is shown in Table E4 in this article's Online Repository at www.jacionline.org.

We next tested for replication of 23 SNPs associated with IgE levels in prior GWASs.[10-14] Fifteen of these SNPs were similarly associated with IgE levels in the GALA II study at nominal significance ($P < .05$): 13 were associated in the same direction as the original study, 1 was associated in the opposite direction, and the direction could not be ascertained from the original study for the final SNP (see Table E5 in this article's Online Repository at www.jacionline.org). Nonetheless, only variants in *RAD50*, *HLA-DRB1*, and *STAT6* were significantly associated with IgE levels after a Bonferroni correction ($P \leq 2.2 \times 10^{-3}$). However, when looking at the gene level (±5 kb), we observed a significant association after Bonferroni correction at a different SNP than initially reported for *IL13* (minimum $P = 7.7 \times 10^{-5}$, rs1295686), *HLA-DRB1* (minimum $P = 1.1 \times 10^{-7}$ for rs41284732), *HLA-DQB1* (minimum $P = 3.5 \times 10^{-6}$ for rs9273395), and *IL4R/IL21R* (minimum $P = 1.5 \times 10^{-6}$ for rs3024667, see Table E6 in this article's Online Repository at www.jacionline.org). We did not find any associated SNPs within or near *DARC*, *FCER1A*, *HLA-G*, or *HLA-G* after correcting for multiple comparisons (see Table E6).

Admixture mapping

We identified 4 admixture mapping peaks whereby local genetic ancestry was significantly associated with IgE levels ($P \leq 4.8 \times 10^{-5}$, Table I). Additional peaks showing a suggestive association are listed in Table E7 in this article's Online Repository at www.jacionline.org. Our most significant peak was located at 6p21.32-p22.1 within the MHC region (see Fig E3 in this article's Online Repository at www.jacionline.org). The minimum P value of the peak was located at rs3094691 in the *HLA-B* gene, where Native American ancestry was associated with lower total IgE levels ($\beta = -0.23$, $P = 4.95 \times 10^{-8}$), and European and African ancestries were associated with higher IgE levels ($\beta = 0.14$, $P = 4.6 \times 10^{-3}$ for European ancestry and $\beta = 0.16$, $P = 1.6 \times 10^{-4}$ for African ancestry, Fig 2). The top of the peak was located 300 kb away from an admixture mapping peak for asthma previously identified in the same study population (GALA II study).[23] A stratified analysis of asthma cases and control subjects showed that the association of Native American ancestry with IgE at 6p21.32-p22.1 was independent of asthma status because the effects were similar in both cases and control subjects ($\beta = -0.23$, $P = 4.8 \times 10^{-5}$ for cases and $\beta = -0.21$, $P = 3.8 \times 10^{-4}$ for control subjects). We further examined whether the association of Native American ancestry with IgE levels at 6p21.33 was mediating our prior association with asthma in the same region.[23] Including IgE level as a covariate in association testing for asthma yielded a result that was still significant (odds ratio, 0.83; 95% CI, 0.74-0.93; $P = 1.6 \times 10^{-3}$ vs odds ratio, 0.78; 95% CI, 0.69-0.87; $P = 1.7 \times 10^{-5}$ for the adjusted and unadjusted models, respectively). Furthermore, a Bayesian network analysis[32] confirmed that the MHC region contains 2 independent

TABLE I. Results of admixture mapping in the GALA II study and replication in the GALA I study

		Discovery GALA II			Replication GALA I		
Band	**Ancestry**	**β**	**95% CI β**	***P* value**	**β**	**95% CI β**	***P* value**
6p21.32-22.1	Native	−0.23	−0.32 to −0.14	$\mathbf{5.0 \times 10^{-8}}$	−0.56	−0.96 to −0.16	$\mathbf{5.7 \times 10^{-3}}$
	African	0.25	0.12 to 0.39	$\mathbf{2.1 \times 10^{-5}}$	0.71	0.28 to 1.14	$\mathbf{1.3 \times 10^{-3}}$
13p22.1-q31.3	African	−0.35	−0.48 to −0.21	$\mathbf{1.0 \times 10^{-6}}$	−0.85	−1.43 to −0.27	$\mathbf{3.8 \times 10^{-3}}$
	European	0.30	0.16 to 0.43	$\mathbf{1.8 \times 10^{-6}}$	0.43	0.05 to 0.80	.025
14q23.2	African	0.25	0.12 to 0.39	$\mathbf{3.0 \times 10^{-5}}$	0.80	0.20 to 1.40	$\mathbf{9.1 \times 10^{-3}}$
22q13.1	African	−0.69	−1.01 to −0.37	$\mathbf{1.9 \times 10^{-5}}$	0.35	−0.25 to 0.94	.252

A total of 4 significant admixture mapping peaks were identified in the GALA II study, of which 3 were significantly replicated in the same direction and with the same ancestry in the GALA I study. Significant *P* values after Bonferroni correction for multiple tests are shown in boldface.

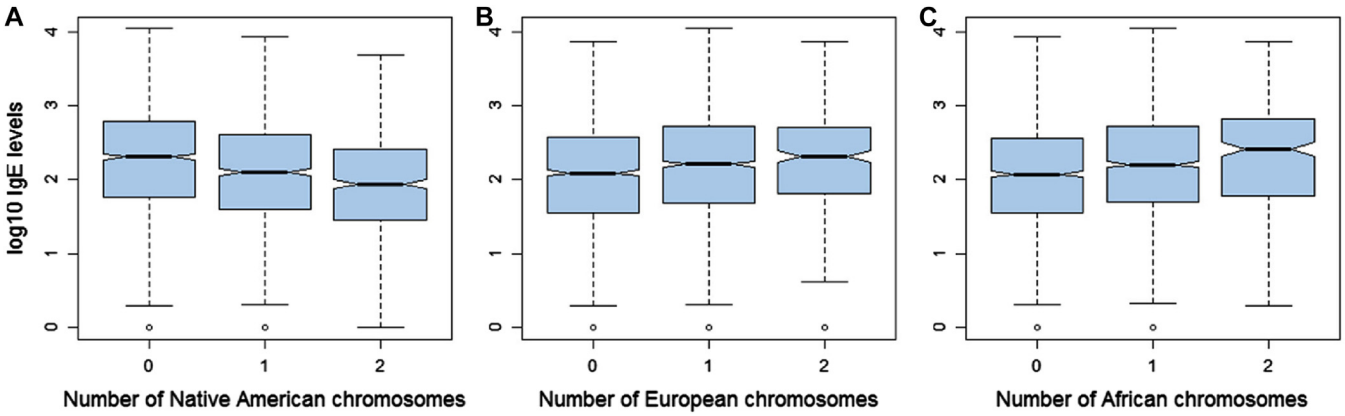

FIG 2. Box plot showing the distribution of IgE levels for each copy of a chromosome of Native American **(A)**, European **(B)**, and African **(C)** ancestry at 6p21.33.

associations with asthma and IgE levels, despite these associations being correlated through linkage disequilibrium (see Fig E4 in this article's Online Repository at www.jacionline.org). The 3 additional admixture mapping peaks detected included an association between local African ancestry and higher IgE levels at 14q23.2 ($\beta = 0.25$, $P = 3.0 \times 10^{-5}$) and between local African ancestry and lower IgE levels at 13p22.1-q31.3 ($\beta = -0.35$, $P = 1.0 \times 10^{-6}$) and 22q13.1 ($\beta = -0.69$, $P = 1.9 \times 10^{-5}$; Table I).

Three of the 4 admixture mapping peaks were replicated in the GALA I study after Bonferroni correction (4 peaks: $P < .013$): 6p21.32-p22.1 ($P = 5.7 \times 10^{-3}$ and $P = 1.3 \times 10^{-3}$ for Native American and African ancestry, respectively), 13p22.1-q31.3 ($P = 3.8 \times 10^{-3}$), and 14q23.2 ($P = 9.1 \times 10^{-3}$, Table I). We then brought forward the 3 peaks showing positive replication in the GALA I study for replication in African Americans from the EVE Consortium studies and used Bonferroni correction for the number of peaks tested (3 peaks: $P < .017$). The peaks at 6p21.32-p22.1 and 14q23.2 were replicated in the combined analysis of 3187 African American subjects from the EVE Consortium studies ($P \leq .017$, see Table E8 in this article's Online Repository at www.jacionline.org).

Fine mapping of admixture mapping peaks

We next performed fine mapping of 3 admixture mapping peaks that showed significant replication in the GALA I study (6p21.32-p22.1, 13p22.1-q31.3, and 14q23.2) through allelic association testing. Twenty-nine SNPs within 6p21.32-p22.1 were significantly associated with IgE levels after Bonferroni correction for the number of genotyped SNPs within the admixture mapping peak (peak-wide significant, $P \leq 8 \times 10^{-6}$; see Table E9 in this article's Online Repository at www.jacionline.org). Further fine mapping with imputed genotypes revealed 90 additional associated SNPs. A total of 39 of the 119 associated SNPs showed nominal replication in the same direction in the GALA I study (see Table E10 in this article's Online Repository at www.jacionline.org), and patterns of linkage disequilibrium were similar between the GALA I and GALA II studies within this region (see Fig E5 in this article's Online Repository at www.jacionline.org). One of the imputed SNPs, located 21 kb 5′ of *HLA-DQA1*, was genome-wide significant in the GALA II study (rs1846190, $P = 3.5 \times 10^{-8}$; Fig 3) and replicated in the same direction in the GALA I study ($P = .003$, meta-$P = 4.6 \times 10^{-10}$). Among the 39 replicated SNPs, 5 additional SNPs reached genome-wide significance when the results from the GALA II and GALA I studies were combined (Table II). Two of these SNPs were further replicated in European Americans (rs113176001, $P = .010$ and rs9270747, $P = .016$) but not in African Americans (see Table E10).

The SNP rs113176001 is located 14 kb 5′ of *HLA-DRB1* within histone modification marks (H3k4me1, H3k9me3, H3k04me1, H3k27ac, and H3k79me2) in lymphoblastoid cells (GM12878) identified by the ENCODE project, and it is in a region that acts as a strong enhancer based on the chromatin state segmentation.[45] Furthermore, rs113176001 was previously identified as a strong eQTL for several proximal genes in Europeans from the 1000 Genomes Project (minimum $P = 3.2 \times 10^{-17}$ for *HLA-DQA1*, see Table E11 in this article's Online Repository at www.jacionline.org) but not in subjects of African descent. rs9270747 is also a strong eQTL for several proximal genes (minimum $P = 1.8 \times 10^{-60}$ for *HLA-DRB5*, see Table E11).

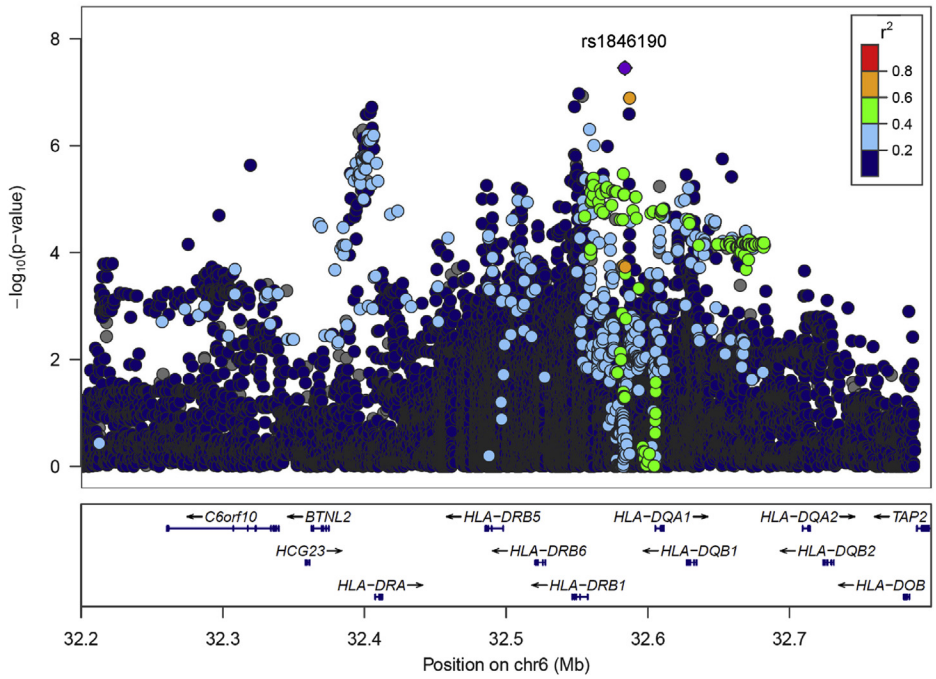

FIG 3. Fine mapping results of 6p21.32-p22.1 in the GALA II study, focusing on the region showing genome-wide significant allelic associations. Included in the plot are $-\log_{10}(P$ values) of association with total serum IgE levels by chromosome position. The most significant SNP is represented by a *diamond*, and the results for the remaining SNPs are color coded to show their linkage disequilibrium with this SNP based on pairwise r^2 values from the Latino populations of the 1000 Genomes Project. SNPs above the dashed line are genome-wide significant ($P \leq 5 \times 10^{-8}$).

TABLE II. Summary of SNPs identified as genome-wide significantly associated with IgE levels through fine mapping of an admixture mapping peak at 6p21.32-p22.1

rs no.	Position*	Gene/closest gene	Allele 1/allele 2†	GALA II study β (95% CI)	GALA II study *P* value	GALA I study β (95% CI)	GALA I study *P* value	Meta-analysis β (95% CI)	Meta-analysis *P* value
rs41284732	32551427	*HLA-DRB1*	T/C	−0.27 (−0.37 to −0.17)	**1.06×10^{-7}**	−0.30 (−0.53 to −0.07)	**.010**	−0.27 (−0.36 to −0.18)	**3.45×10^{-9}**
rs186715542	32558702	3′ of *HLA-DRB1*	C/T	0.24 (0.15 to 0.33)	**4.96×10^{-7}**	0.26 (0.02 to 0.50)	**.034**	0.25 (0.16 to 0.33)	**4.89×10^{-8}**
rs9270747	32568292	3′ of *HLA-DRB1*	A/G	−0.19 (−0.27 to −0.11)	**3.42×10^{-6}**	−0.33 (−0.53 to −0.13)	**.002**	−0.21 (−0.29 to −0.14)	**3.56×10^{-8}**
rs113176001	32571483	5′ of *HLA-DRB1*	G/C	−0.29 (−0.41 to −0.17)	**1.03×10^{-6}**	−0.36 (−0.63 to −0.09)	**.008**	−0.30 (−0.41 to −0.20)	**3.04×10^{-8}**
rs1846190	32583813	5′ of *HLA-DQA1*	G/A	0.22 (0.14 to 0.30)	**3.51×10^{-8}**	0.29 (0.10 to 0.48)	**.003**	0.23 (0.16 to 0.30)	**4.63×10^{-10}**
rs557011	32587013	5′ of *HLA-DQA1*	C/T	0.21 (0.13 to 0.29)	**1.28×10^{-7}**	0.27 (0.07 to 0.47)	**.007**	0.21 (0.14 to 0.29)	**3.55×10^{-9}**

P values of .05 or less are shown in boldface.
*According to the hg19 assembly.
†Allele 1 represents the allele for which effect size is reported.

Within 13p22.1-q31.3, a total of 6 SNPs were peak-wide significantly associated with IgE levels in the GALA II study (minimum $P = 3.9 \times 10^{-6}$, see Tables E9 and E12 and Fig E6 in this article's Online Repository at www.jacionline.org), but none of them were replicated in the rest of studies. However, these SNPs showed high variability in allele frequency across studies/populations (see Fig E7 in this article's Online Repository at www.jacionline.org). Furthermore, 4 of the SNPs had low-quality imputation scores in 1 or more studies (info score < 0.4).

Allelic association testing of SNPs within 14q23.2 in the GALA II study did not reveal any significantly associated genotyped SNPs after Bonferroni correction (see Table E9). The most significant SNP was rs2012961 ($P = 1.4 \times 10^{-4}$, see Fig E8 in this article's Online Repository at www.jacionline.org), which is located in the 3′ untranslated region of the ras homolog family member J gene *(RHOJ)* and coincides with the top of the admixture mapping peak. This SNP was replicated in the GALA I study ($P = .019$) but not in African Americans or European Americans in the EVE Consortium (Table E12). Imputation in the GALA II study revealed an additional SNP that was slightly more significant than the strongest associated genotyped SNP ($P = 1.2 \times 10^{-4}$ for rs10129357 vs $P = 1.4 \times 10^{-4}$ for rs2012961). The imputed SNP was subsequently replicated in European Americans in the EVE Consortium ($P = .024$).

We then tested for allelic association within the admixture mapping peaks identified in the GALA II study in African Americans and European Americans under the hypothesis that causal variants might be better tagged by different SNPs in other populations (see Table E13 in this article's Online Repository at www.jacionline.org). In African Americans an intronic SNP within 14q23.2 was peak-wide significantly associated with IgE levels after Bonferroni correction for 6511 tests (rs1741099, $\beta = 0.17$, $P = 3.7 \times 10^{-6}$). The association was replicated in all of the non–African American samples combined ($\beta = 0.08$, $P = .011$). The SNP rs1741099 is located in intron 1 within the gene encoding the glycoprotein hormone beta 5 (*GPHB5*; see Fig E9 in this article's Online Repository at www.jacionline.org) and is 23 kb away from rs2012961, the most associated SNP in Latinos. We did not find any significant associations in European Americans after adjusting for multiple tests (minimum $P = 1.1 \times 10^{-4}$ for rs10483752 at the potassium voltage-gated channel, subfamily H [eag-related], member 5 [*KCNH5*]; see Table E13).

Association analysis with related phenotypes

SNPs from *STAT6* and *RAD50* were nominally associated with asthma, and SNPs from *HLA-DQA1* were nominally associated with atopy and rhinitis (see Table E14 in this article's Online Repository at www.jacionline.org). The SNP in *GPHB5* was nominally associated with asthma, eczema, and allergic rhinitis (see Table E14). One SNP from the *IL4R/IL21R* locus showed an interaction with asthma status at a P value of less than .05 (see Table E15 in this article's Online Repository at www.jacionline.org).

Exon sequencing of candidate genes

Exon sequencing of *HLA-DQB1*, *HLA-DRB5*, and *ZNF365* was performed in 1395 Puerto Ricans from the GALA II study (856 asthma cases and 539 control subjects). Gene-based association testing revealed a significant contribution of multiple nonsynonymous variants to IgE levels in *HLA-DQB1* (Sequence Kernel Association Test, $P = 2.1 \times 10^{-3}$; see Fig E10 in this article's Online Repository at www.jacionline.org) but not in *HLA-DRB5* ($P = 1.0$) or *ZNF365* ($P = .245$). No additional single variants were identified as being more strongly associated with IgE levels than those already identified through GWAS and imputation.

DISCUSSION

In this study we performed a GWAS of IgE levels in Latinos and identified a novel genome-wide significant allelic association at *ZNF365*. We also found that the majority of prior associations identified from GWASs primarily in European populations were applicable to Latino populations at the SNP level, gene-based level, or both. We further performed the first admixture mapping of IgE levels and identified a strong association between local ancestry at the MHC region and total serum IgE levels, which was replicated in Latinos from the GALA I study and in African Americans from the EVE Consortium. Allelic association testing within the MHC peak in the GALA II study revealed several SNPs associated with IgE levels that replicated in the GALA I study, 6 of which were genome-wide significant in either the GALA II study alone or in a meta-analysis of the 2 studies. Two additional admixture mapping peaks identified in the GALA II study were replicated in the GALA I study (13p22.1-q31.3 and 14q23.2), and one of these peaks was further replicated in African Americans (14q23.2). Fine mapping of these 2 regions revealed allelic associations within the *KCNH5-RHOJ-GPHB5* genes at 14q23.2 in a combination of Latinos, European Americans, and African Americans.

We performed admixture mapping in addition to a conventional GWAS and identified additional associations with IgE levels. We predicted this would be a powerful approach because of the observed differences in IgE levels among Latinos, African Americans, and European Americans[16-19] and the association between genomic African ancestry and IgE levels.[20,21] Our results demonstrate that local ancestry can capture additional important genetic variation that is not attainable through conventional GWASs. As expected, individual alleles showing an association with IgE levels within the admixture mapping peaks had an enormous variation in minor allele frequency across populations (see Fig E7). Exon sequencing further identified an association of pooled nonsynonymous variants with IgE levels in a gene implicated through admixture mapping *(HLA-DQB1)* but not in a gene implicated through conventional GWASs *(ZNF365)*. Thus far, our results suggest that the association detected with local ancestry at 6p21.32-p22.1 is driven by a combination of both common and rare variation.

ZNF365 encodes a protein involved in mitosis and genomic stability.[46] Genetic variation in *ZNF365* was associated with atopic dermatitis in Japanese and Chinese populations[47,48] but not in Europeans.[49] Atopic dermatitis is an allergic disease modulated through IgE, and therefore our association with IgE levels reinforces the role of *ZNF365* in atopic phenotypes. However, we note that the association of the genome-wide significant indel in *ZNF365* was in the opposite direction in the GALA I study compared with the GALA II study. Allele frequencies were similar among studies, imputation performed well (info score ≥ 0.9), and we found no significant interaction with asthma. Therefore our result could be attributed to differences in recruitment of patients or gene-environment interactions. The associated indel is located in the first intron of transcript variant D of *ZNF365*, an isoform the differential expression of which has been previously associated with Crohn disease.[50] The combined set of variants within the first intron of *ZNF365* transcript variant D with a P value of less than 10^{-6} showed a 2.6-fold enrichment in enhancers in the lymphoblastoid cell line GM12878 ($P = .027$) and a 6.7-fold enrichment in DNase sensitivity sites in $CD20^{+}$ B cells ($P = .036$). Therefore we speculate that variation associated with IgE levels in the first intron of *ZNF365* affects the expression, splicing, or both of *ZNF365* and might ultimately affect recombination processes needed for the differentiation of B cells in IgE-producing cells, as has been proposed for *RAD50*.[51]

We identified genome-wide significant associations through admixture mapping and fine mapping in the MHC region. Although this region was already known to contain genes that influence IgE levels,[10,11,13] in this study we identified an important role of local genetic ancestry. In addition, our genome-wide significant associations are different from those previously described in GWASs involving European[10,11,13] or Asian[14] populations. Moreover, for the first time, we implicated variation in *HLA-DQA1* in affecting IgE levels. The most

significantly associated SNP (rs113176001) is located within the intergenic region between *HLA-DRB1* and *HLA-DQA1* and is a strong eQTL for *HLA-DQA1*. Interestingly, this SNP was only an eQTL in lymphoblastoid cells in European but not African subjects from the 1000 Genomes Project. Furthermore, it was not significantly associated with IgE levels in African Americans from the EVE Consortium, although the direction of effect was the same. This could be due to variation in allele frequency between populations because the minor allele of this SNP is more frequent in Latino and European populations from the 1000 Genomes Project (25% and 22% for the C allele, respectively) than in African populations (14%, see Fig E3).

Using admixture mapping, we also uncovered an association of African ancestry at 13p22.1-q31.3 with lower IgE levels. Fine mapping revealed significant allelic associations in the GALA II study that did not replicate in the GALA I study, perhaps suggesting the presence of false-positive associations, although this might also be due to reduced statistical power from the smaller sample size in the GALA I study. African ancestry at 14q23.2 was associated with higher IgE levels both in Latinos and African Americans. Linkage studies previously identified 14q23 as a locus affecting IgE levels.[52,53] However, no associations of specific genes have been reported. Fine mapping of 14q23 in multiethnic groups narrowed the association to 3 candidate genes: *KCNH5* and *RHOJ* through variants nominally associated in Latinos and *GPHB5* in African Americans. These 3 genes are expressed by immune cells, such us T lymphocytes, B cells, and plasma cells, but they have not been associated before with IgE levels or allergic phenotypes. Therefore the role of genetic variation in *KCNH5*, *RHOJ*, and *GPHB5* on IgE levels requires additional study.

An important aspect of our study is that fine mapping of candidate regions by using imputed genotypes from the 1000 Genomes Project boosted our ability to detect novel associations. However, a GWAS using imputed data did not reveal any additional associations from those already identified in our fine mapping of regions identified by GWAS/admixture mapping (data not shown). One limitation of our study is that we did not account for possible interactions between genotype and early-life exposure to allergens. In addition, IgE levels were measured by using different methods across the replication studies, which might account for the lack of the replication of some of the findings. Furthermore, we note that Latinos are a heterogeneous group, and therefore findings from this study might not be generalizable to all Latino populations. Finally, future studies will be needed to disentangle the association at the MHC region by evaluating the association of classic alleles. However, better reference panels for HLA imputation need to be developed for Latino populations.

In summary, we confirmed associations at 6 loci previously associated with total serum IgE levels and identified novel associations at *ZNF365*, *HLA-DQA1*, and 14q23.2, all of which are likely to play an important role in total serum IgE levels in Latinos. Sequencing of GWASs and admixture mapping peaks, including noncoding regions, followed by functional studies is required to identify the causal variation behind these associations.

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Key messages

- **Although differences in IgE levels have been reported between racial/ethnic groups, GWASs have predominantly focused on populations of European descent.**
- **We performed a GWAS and admixture mapping in Latinos and found novel associations at 3 genes/loci, including *ZNF365*, *HLA-DQA1*, and 14q23.2.**
- **Our results demonstrate how GWASs and admixture mapping in diverse populations can identify novel genetic variation that is relevant to the health of global populations.**

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