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A Meta-analysis of Genome-wide Association Studies for Serum Total IgE in Diverse Study Populations

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Clinical Implications: This study suggests that many of the genetic risk factors for serum total IgE are shared among North American race-ethnic groups.

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Abstract

Background—Immunoglobulin E (IgE) is both a marker and mediator of allergic inflammation. Despite reported differences in serum total IgE levels by race-ethnicity, African American and Latino individuals have not been well represented in genetic studies of total IgE.

Objective—To identify the genetic predictors of serum total IgE levels.

Methods—We used genome wide association (GWA) data from 4,292 individuals (2,469 African Americans, 1,564 European Americans, and 259 Latinos) in the EVE Asthma Genetics Consortium. Tests for association were performed within each cohort by race-ethnic group (i.e., African American, Latino, and European American) and asthma status. The resulting p-values were meta-analyzed accounting for sample size and direction of effect. Top single nucleotide polymorphism (SNP) associations from the meta-analysis were reassessed in six additional cohorts comprising 5,767 individuals.

Results—We identified 10 unique regions where the combined association statistic was associated with total serum IgE levels (P-value $<5.0\times10^{-6}$) and the minor allele frequency was 5% in two or more population groups. Variant rs9469220, corresponding to *HLA-DQB1*, was the most significantly associated SNP with serum total IgE levels when assessed in both the replication cohorts and the discovery and replication sets combined (P-value = 0.007 and 2.45×10^{-7}, respectively). In addition, findings from earlier GWA studies were also validated in the current meta-analysis.

Conclusion—This meta-analysis independently identified a variant near *HLA-DQB1* as a predictor of total serum IgE in multiple race-ethnic groups. This study also extends and confirms the findings of earlier GWA analyses in African American and Latino individuals.

Keywords

meta-analysis; genome wide association study; total immunoglobulin E; race-ethnicity; continental population groups

INTRODUCTION

Immunoglobulin E (IgE) is an important mediator in allergic inflammation and is often elevated in individuals with atopic conditions, such as asthma.[1–3] Recently published genome wide association studies (GWAS) for asthma and serum total IgE levels suggest that there are some, but not many, overlapping top-hit single nucleotide polymorphisms (SNPs) in genes associated with these phenotypes.[4–6] The independence (i.e., lack of genetic pleiotropy) of these two phenotypes is also supported by minimal shared variance between the heritable components of serum total IgE and airway responsiveness.[7] In addition, although environmental exposures influence total IgE levels, studies in twins suggest that genetic inheritance accounts for the majority of variation in levels between individuals.[8;9]

Serum total IgE levels differ by population group in the U.S. with higher levels reported in both African American and Latino individuals when compared with non-Hispanic white individuals (henceforward referred to as European Americans).[10–13] As genetic ancestry has been shown to be associated with total IgE levels, it is possible that these population-level differences have some genetic underpinnings.[14] This is also supported by heterogeneity in linkage signals for total IgE among these three population groups.[15] However, despite these potential differences, African American and Latino individuals have not been well represented in genetic studies of total IgE to date.

The EVE consortium comprises nine research groups across the U.S. with genome wide genotype data on individuals with and without asthma. The assembled study participants are broadly representative of three major population groups (i.e., African American, European American, and Latino individuals) in North America and have data on asthma-associated phenotypes, including serum total IgE. We describe here the results of a meta-analysis of GWAS for serum total IgE, combining results from the various EVE investigators. Associations were first determined among subgroups of individuals defined by asthma status and self-identified race-ethnicity before combining so as to minimize the potential confounding effects of these characteristics.

METHODS

Study populations

The EVE consortium comprises nine investigative teams throughout the U.S., each with genome wide association data for asthma from case-control, trio, or extended family studies.[16] All of the cohorts represented in the meta-analysis (i.e., the discovery set) were part of the EVE consortium, and each of these individual study populations has been described in detail previously.[17–25] These study populations are broadly representative of the major North American population groups and were recruited through clinics and health systems in the U.S., Puerto Rico, Mexico, and Barbados. All studies included in the current analysis were approved by their respective institutional review boards.

Only the EVE samples in which the participants had serum total IgE measured at the time of screening or enrollment were included in the current meta-analysis. These included the following studies: the Study of Asthma Phenotypes and Pharmacogenomic Interactions by Race-ethnicity (SAPPHIRE), the Genetic Research on Asthma in the African Diaspora (GRAAD), Genetics of Asthma in Latino Americans (GALA), the Childhood Asthma Management Program (CAMP), the Childhood Asthma Research and Education Network (CARE), the Chicago Asthma Genetics Study (CAG), the National Heart, Lung, and Blood Institute (NHLBI) Collaborative Studies of the Genetics of Asthma (CSGA), and the Severe Asthma Research Program (SARP). The latter three studies make up the NHLBI-supported SNP Typing for Association with Multiple Phenotypes from Existing Epidemiologic Data (STAMPEED) consortium (heretofore collectively referred to by that acronym).

SAPPHIRE is an ongoing prospective cohort study to determine the genetic determinants of inhaled corticosteroid response.[17;18] Participants were aged 12–56 years, had a physician diagnosis of asthma, demonstrated bronchodilator reversibility (>12% increase in forced expiratory volume at one second [FEV_1]), and had no prior diagnosis (in the electronic medical record or by patient report) of chronic obstructive pulmonary disease (COPD) or congestive heart failure (CHF). All patients were recruited from a single, large health system covering southeast Michigan. A subset of these individuals was genotyped using the Affymetrix 6.0 GeneChip Array (Affymetrix, Inc., Santa Clara, California). Controls for SAPPHIRE were from the Wayne County Health Environment Allergy and Asthma Longitudinal Study, and included expectant women age 21 years from the Detroit metropolitan area and receiving care from the same health system. This group was genotyped using the Affymetrix 5.0 GeneChip Array or the 500K Mapping Array.

The GRAAD-AA study comprised African American individuals with asthma (self-reported) and non-asthmatic control patients from the Baltimore-Washington D.C. area.[19] The GRAAD-AC study consisted of extended families from Barbados with at least one asthma proband.[19] In this study, a diagnosis of asthma required a self-reported history, physician diagnosis, and a history of wheezing without an upper respiratory infection. Individuals were genotypied on the Illumina HumanHap650Y versions 1 and 3 BeadChips (Illumina, Inc., San Diego, California).

GALA is a trio study including asthma probands age 8–40 years with a physician diagnosis of mild to moderate-severe asthma and symptoms at least twice in the two years preceding enrollment.[20] Individuals were recruited from sites in San Francisco, New York City, Puerto Rico, and Mexico City. Individuals were genotyped on the Affymetrix 6.0 GeneChip Array.

The CAMP subjects were part of a multi-center clinical trial of children with mild to moderate asthma and airway responsiveness by methacholine challenge (20% drop in FEV_1 with 12.5 mg/dl of methacholine).[23] While parents of these children were also recruited for this trio study, only the children with total IgE data were included in the current analysis. Individuals were genotyped on the Illumina HumanHap500 version 3 BeadChip.

CARE represents a series clinical trials, 5 of which contributed to the current meta-analysis (PEAK,[26] PACT,[27] CLIC,[28] AIMS,[29] and MARS[30]). All participants were children with physician diagnosed asthma. Parents of these subjects were also recruited to compose a trio study, but the only the children for whom we had total IgE data were included in this analysis. Individuals were genotyped using the Affymetrix 6.0 GeneChip array.

CAG and CSGA samples comprise both children and adults with asthma (physician diagnosis, symptoms, and airway responsiveness by methacholine challenge or bronchodilator reversibility). Individuals in these studies were recruited from multiple

locations, but only those recruited from clinics at the University of Chicago, University of Maryland – Baltimore, and Wake Forest University and who had genome wide genotype data were included in the current analysis. SARP included individuals with mild to severe asthma.[31] Non-asthmatic control subjects were recruited from the same clinic sites for these studies. The subjects were genotyped on the Illumina 1M version 1 BeadChip.

Meta-analysis for serum total IgE

Given the different platforms used to genotype the EVE cohorts, imputation was used to create a common and near complete set of SNP genotypes across all groups. Each research group used the program, MACH,[32] to impute genotypes in their respective study population(s) using the reference panels from HapMap phase 2, release 21. For European American individuals, haplotypes from the CEPH European Americans of Northern and Western European ancestry (CEU) were used as the reference. For African American and African Caribbean individuals, both the CEU and the Yoruba of West African (YRI) haplotypes served as reference. For Latino individuals, the haplotypes from all of the original HapMap population groups (i.e., CEU, YRI, Japanese from Tokyo [JPT], and the ethnic Han Chinese from Beijing [CHB]) were used as reference. Poorly imputed SNPs with MACH r-squared values <0.3 were removed from the analysis.

For analysis, study subjects were stratified by study cohort, race-ethnicity (i.e., African Caribbean and African American combined, European American, and Latino), and asthma status. The dependent variable, serum total IgE, was logarithmically (natural log) transformed to normalize its distribution and diminish the effect of outliers; five individuals with total IgE values <2 IU/ml were also excluded from the analysis. As has been done for other genetic analyses,[33] we used Studentized residuals to standardize the distributions of log-transformed IgE values across race-ethnic groups, asthma disease status, and study populations. For each within study population group, we generated Studentized residuals adjusted for age and sex, whereby the residuals represented the remaining variation in total IgE after adjustment. Because these residuals were normally distributed, these steps ensured a comparable scale for the regression coefficient summarizing the association between each SNP and total IgE, thus limiting bias in the meta-analysis arising from distributional differences in total IgE levels across groups. These residuals were then used as the primary phenotype for association with the allele dosage estimates for each genotype. We assumed an additive genetic model with the reference allele coded as zero. To account for underlying population structure, study-specific genome wide principal components generated by the program EIGENSOFT were included as covariates.[34] Given the extended pedigree structure of GRAAD-AC, a linear mixed effects model using a kinship matrix approach was employed for this cohort;[35] this method corrects for familial correlation (both known and unknown) by estimating the empirical kinship between all pairs of subjects.

We used the analytic software, METAL,[36] to perform the meta-analysis. This program used an inverse normal approach to combine stratum specific p-values, which accounted for both the direction of effect and the sample size of each stratum. The meta-analysis was performed for the overall sample and within the race-ethnic groups (i.e., African Caribbean and African American individuals combined, European Americans, and Latinos). The most significant SNP associations (P value $<5.0 \times 10^{-6}$) were promoted for replication if they were informative in at least two of the three race-ethnic groups (i.e., a minor allele frequency 5%). This threshold was similar to that suggested by others for genome-wide association studies,[37] but was less stringent than the Bonferroni corrected value (P value $<5.0 \times 10^{-8}$) which may overly conservative. We elected to use the former so as to provide a feasible number of SNPs for assessing replication. When multiple SNPs in a region met this criterion, we selected the polymorphism with the greatest overall statistical significance. We

also assessed for heterogeneity of the top SNP associations by race-ethnicity and asthma disease status using the Cochran's Q-test as implemented in METAL.[36;38]

Replication populations and analysis

The top 10 signals were replicated in six case-control and population-based samples from the U.S and Canada and a founder population in the U.S. The U.S. replication populations included a separate group of individuals from SAPPHIRE,[39] the Gene-Environments and Admixture in Latino Americans (GALA II) study, and the Study of African Americans, Asthma, Genes & Environments (SAGE [U.S.]).[40] The Canadian cohorts included the Canadian Asthma Primary Prevention Study (CAPPS)[41;42] and the Study of Asthma Genes and the Environment (SAGE [Canada]).[42;43] The U.S. founder population consisted of Hutterites who live in South Dakota.[44]

The SAPPHIRE study participants included in the replication were those without genome wide association data who were age 12–56 years, had a physician diagnosis of asthma, and no prior diagnosis of COPD or CHF. Replication controls were also age 12–56 years; had no prior diagnosis of asthma, COPD, or CHF; and were recruited within the same health care system.

The GALA II study is a large case-control study recruiting Latino patients with and without asthma (physician diagnosed) from clinical sites in San Francisco, New York City, Houston, Chicago, and Puerto Rico. Individuals were recruited at age 8–21 years. The SAGE (U.S.) study was overseen by the same research team, and recruited African American individuals with and without a physician diagnosis of asthma from the San Francisco Bay area. Case patients were age 8–40 years and had physician diagnosed asthma. Control patients in both GALA II and SAGE were enrolled from the same clinics concurrently and had no prior diagnosis of allergies, asthma, lung disease, symptoms consistent with asthma within the preceding 2 years, and <10 pack-year smoking history.

The Canadian SAGE study was a population-based birth cohort consisting of individuals born in Manitoba in 1995. From this group, a nested case-control study was selected, representing children with and without pediatrician diagnosed asthma. Serum total IgE was measured between the ages of 7–10 years. CAPPS, another birth cohort, included infants born between October 1994 and August 1996 who were deemed to be at high risk for developing allergies as a result of ≥1 1st degree relative with asthma or ≥2 first degree relatives with an IgE-mediated allergic disease.

The founder population comprised the Schmiedeleut Hutterites residing in primarily South Dakota. This extended pedigree has been used in prior investigations of allergy and asthma.[44–46]

Replication genotype data was generated from either allelic discrimination (TaqMan®, Applied Biosystems, Foster City, California) or commercially available high-throughput arrays. For the SAPPHIRE and SAGE cohorts all replication SNPs were genotyped by allelic discrimination. In GALA II genome wide array results were available from the Axiom LAT array (Affymetrix, Inc., Santa Clara, California) for rs9469220 and rs16977747, and the remaining SNP were genotyped using TaqMan. In the two Canadian cohorts, rs321588, rs7751374, rs10124954, and rs6499255 were genotyped on the Illumina Human610-Quad array; rs9469220, rs537526, and rs16977747 were imputed using MACH; rs2885872 was a genotyped proxy (CEU r^2=1.0) used for rs2363709; and rs10043454 and rs4355582 were imputed proxies used for rs13361473 and rs10944017, respectively. Amongst the Hutterites, rs9469220, rs7751374, rs10124954, rs537526, and rs16977747 were genotyped on the Affymetrix 6.0 GeneChip, and rs613614, rs2101567, rs9314043, and

rs11075734 were used as genotype proxies for rs321588, rs2363709, rs13361473, and rs6499255, respectively.

We applied a similar analytic approach as used in the discovery cohorts to the assessment of the replication data. Groups were stratified according to cohort, race-ethnicity, and asthma status. Standardized residuals from the linear models associating natural log transformed serum total IgE levels with age and sex were used in second stage models in association with replication genotypes. The association with genotype was assessed assuming an additive genetic model. We again used METAL[36] to combined stratum specific p-values. Analyses were performed for the overall replication sample and within groups defined by race-ethnicity (i.e., for European American, African American, and Latino individuals).

RESULTS

The characteristics of the six study groups in the genome wide meta-analysis of serum total IgE levels are shown in Table 1 (individuals in GRAAD recruited from the U.S. and the Caribbean are shown separately). These cohorts comprised 4,292 study subjects which ranged in age from 1 to 84 years. The combined group included 2,425 (56.5%) females and 2,754 (64.1%) with a history of asthma. The race-ethnic breakdown of the total group included 2,469 (57.4%) African American and African Caribbean individuals, 259 (6.0%) Latino individuals, and 1,564 (36.4%) European American individuals. The distribution of serum total IgE levels by race-ethnicity, asthma status, and study is shown in the online supplement (eTable 1).

Association for total IgE was performed within groups stratified by race-ethnicity, asthma status, and study cohort. Within the cohorts with a single population group represented (i.e., SAPPHIRE, GRAAD-AC, GRAAD-AA, GALA, and CAMP), we stratified by asthma status alone. Association statistics were meta-analyzed accounting for the direction of the effect and sample size. The overall association results and the associations within each race-ethnic group are shown in Table 2 (parameter estimates for these associations are shown in eTable 2 of the online supplement). The Manhattan plot for the genome wide meta-analysis is shown in Figure 1 and the quantile-quantile plot is shown eFigure 1 of the online supplement. Ten distinct regions were identified where the combined P-value was $<5.0 \times 10^{-6}$ and the association was informative in 2 population groups. Most of the regions associated with total IgE levels were novel with the exception of *HLA-DQB1*.

Six study populations consisting of 5,767 individuals were available to replicate the findings of the discovery set (Table 3). The replication set comprised 2,961 (51.3%) African American individuals, 1,477 (25.6%) Latino individuals, and 1,329 (23.0%) European American individuals; 3,930 (68.1%) had a history of asthma. The association statistics for replication set were combined in a manner analogous to the discovery set. As shown in Table 4, of the ten SNPs analyzed for replication, only rs9469220 near *HLA-DQB1* reached marginal significance (P-value = 0.0074 [replication set]; P-value = 2.45×10^{-7} [combined discovery and replication set]) (parameter estimates for these associations are shown in eTable 3 of the online supplement). There was also some evidence for possible heterogeneity at rs16977747 on chromosome 17 by population group and asthma status (i.e., strongest association for both Latino individuals and those with asthma – eTables 4 and 5 in the online supplement).

We also assessed variants in genes described in earlier genome wide association studies of serum total IgE levels (Table 5). We found that many of the genes (and variants) identified in these earlier studies replicated in the current meta-analysis. Genes with evidence of replication in all of our study groups combined included *DARC*, *FCER1A*, *RAD50*, *IL13*,

HLA-DQA2, and *STAT6*. Not surprisingly, some of the variants showed differences in statistical significance by population group, whereas others (e.g., rs2858331 in *HLA-DQA2*) showed a consistent pattern in all population groups. Interestingly, the variant, rs2858331, which has been ascribed to *HLA-DQA2*,[47] is located ~20 kilobases (kb) from our top hit, rs9469220. Figure 2 shows the linkage disequilibrium (LD) between rs9469220 and rs2858331 and the other SNPs in the HLA-DR/DQ region. eTable 6 in the supplement shows the SNP association statistics for polymorphisms where we had data and which were located within 20 kb of the transcription start and stop site for genes shown in Table 5.

DISCUSSION

We are aware of two genome wide association studies[4;47] and one genome wide meta-analysis examining genetic variants associated with serum total IgE levels.[6] However, to our knowledge this is the first of such studies to include substantial numbers of participants who are not primarily European in ancestry (i.e., African American and Latino individuals).

Our findings confirm the role of variants in the class II major histocompatibility complex (MHC) region on serum total IgE levels. In particular, we found that a polymorphism, rs9469220, located between *HLA-DQB1* and *HLA-DQA2* was associated with total IgE levels. The diversity of our study population further supported the importance of this locus on IgE levels, as the relationship was consistent across multiple population groups and was robust to differences in asthma-disease status.

Moffatt and colleagues as part of the GABRIEL (A Multidisciplinary Study to Identify the Genetic and Environmental Causes of Asthma in the European Community) Consortium also recently described markers around *HLA-DRB1* and *HLA-DQB1* to be associated with total IgE levels, although the latter was more strongly associated with asthma.[6] A recent GWAS of participants enrolled in the Framingham Study also found that a polymorphism just upstream of *HLA-DQA2* (rs2858331) was significantly associated with total IgE levels.[47] Others testing more limited numbers of SNPs have found relationships between polymorphisms in the HLA-DR/DQ region and IgE levels.[48;48;49] Therefore, our results support the findings of these earlier studies and extend them to encompass most major North American population groups.

Total IgE production is promoted through elaboration of type 2 helper T cell (Th2) cytokines, such as interleukin (IL)-4 and IL-5.[50] Type 1 helper T cell (Th1) and Th2 activation may in turn depend on the number of MHC class II molecules involved in presentation and the presence or absence of co-stimulation through CD28.[51] Curiously, querying gene expression results from lymphoblastoid cell lines derived from HapMap individuals,[52] we found that our most significant polymorphism in the HLA-DR/DQ region, rs9469220, is related to the expression of a number of MHC class II molecules. This same SNP has also been shown to be associated with Crohn's disease,[53] which is considered at least in part to be a Th1 condition.[54]

We found evidence for replication in genes previously identified in other genome wide analyses and candidate gene studies as being associated with total IgE levels. As shown in Table 5, these genes included *DARC*,[47;55] *FCER1A*,[4;6;47] *RAD50*,[4;49] *IL13*,[4;6;47;49;56] *HLA-DQA2*,[47] *STAT6*,[4;6;47;57] and *IL4R/IL21R*.[6] Most importantly, we now demonstrate that these relationships are present in multiple population groups.

We also identified at least 2 other loci (rs2363709 on Chromosome 3 and rs16977747 on Chromosome 17) that were associated with serum total IgE levels with possible heterogeneous associations across population groups and disease state. Further studies will

be needed to assess whether these represent true ancestry-specific or asthma-specific (or non-asthma specific) determinants of IgE levels.

This study was not without limitations. First, to remove the potential confounding influence of race-ethnicity, asthma-status, and study cohort, we first stratified our analytic groups by these categories and then recombined the resultant association statistics via meta-analysis. Therefore, despite our large overall study size, the power within each population-specific stratum was limited. Second, although we accounted for the important confounders such as sex and age,[58] many other factors which can influence IgE levels were not available for inclusion in our models, such as the season in which an IgE sample was drawn,[59;60] use of systemic corticosteroids, and exposure to tobacco smoke.[11;61] While these missing factors may have confounded our analysis, it is heartening to see that we could replicate many of the previously described associations. In addition, we cannot say with certainty that the variants we identified by association are causally related to IgE levels; rather, these polymorphism may be in LD with the true causal variant. Because patterns of LD may vary by race-ethnicity, it is also possible that the true causal variant still differs by population group.[62] Determining these causal variants will likely require additional, finer scale genotyping and follow-up functional studies.

In summary, our findings provide further evidence for a role of the HLA-DR/DQ region in serum total IgE levels. Importantly, this study suggests that this region has similar determinative import in European American, African American, and Latino individuals. Our study also replicates many of the previously identified genetic associations with total IgE in these three population groups. Preliminary evidence for genetic predictors which vary by race-ethnicity and asthma status will need to be replicated in the respective population groups. Nevertheless, this study underscores the need to study diverse populations so as to identify both shared and group-specific genetic predictors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Abbreviations

HLA   Human leukocyte antigen

IgE   Immunoglobulin E

GWAS   Genome wide association study

LD   Linkage disequilibrium

MHC   Major histocompatibility complex

SNP   Single nucleotide polymorphism

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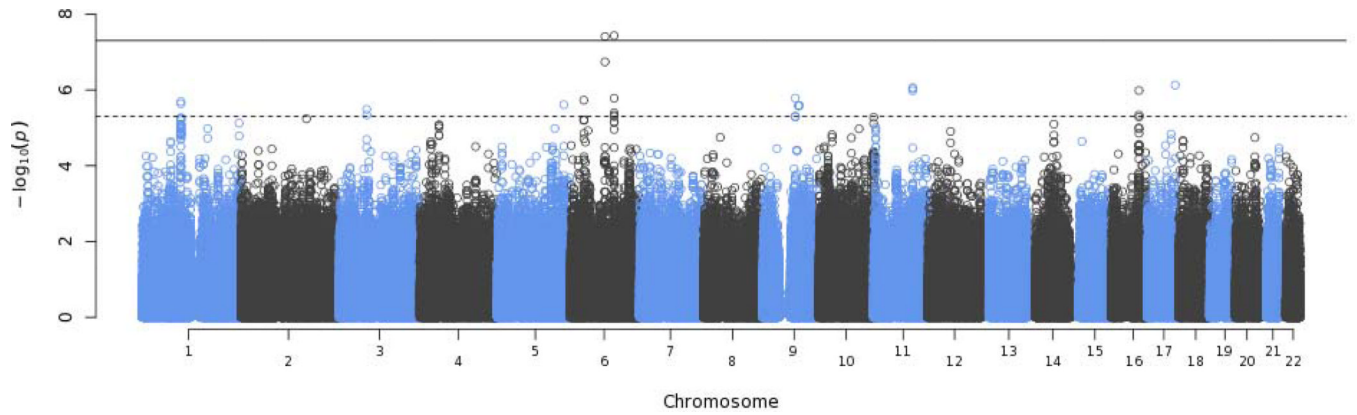
Figure 1.
Manhattan plot of the genome wide association results for serum total IgE from the meta-analysis. The significance level used to promote single nucleotide polymorphisms for replication ($P < 5.0 \times 10^{-6}$) is denoted by the dashed line. The solid line shows the genome wide significance level of $P < 5.0 \times 10^{-8}$.
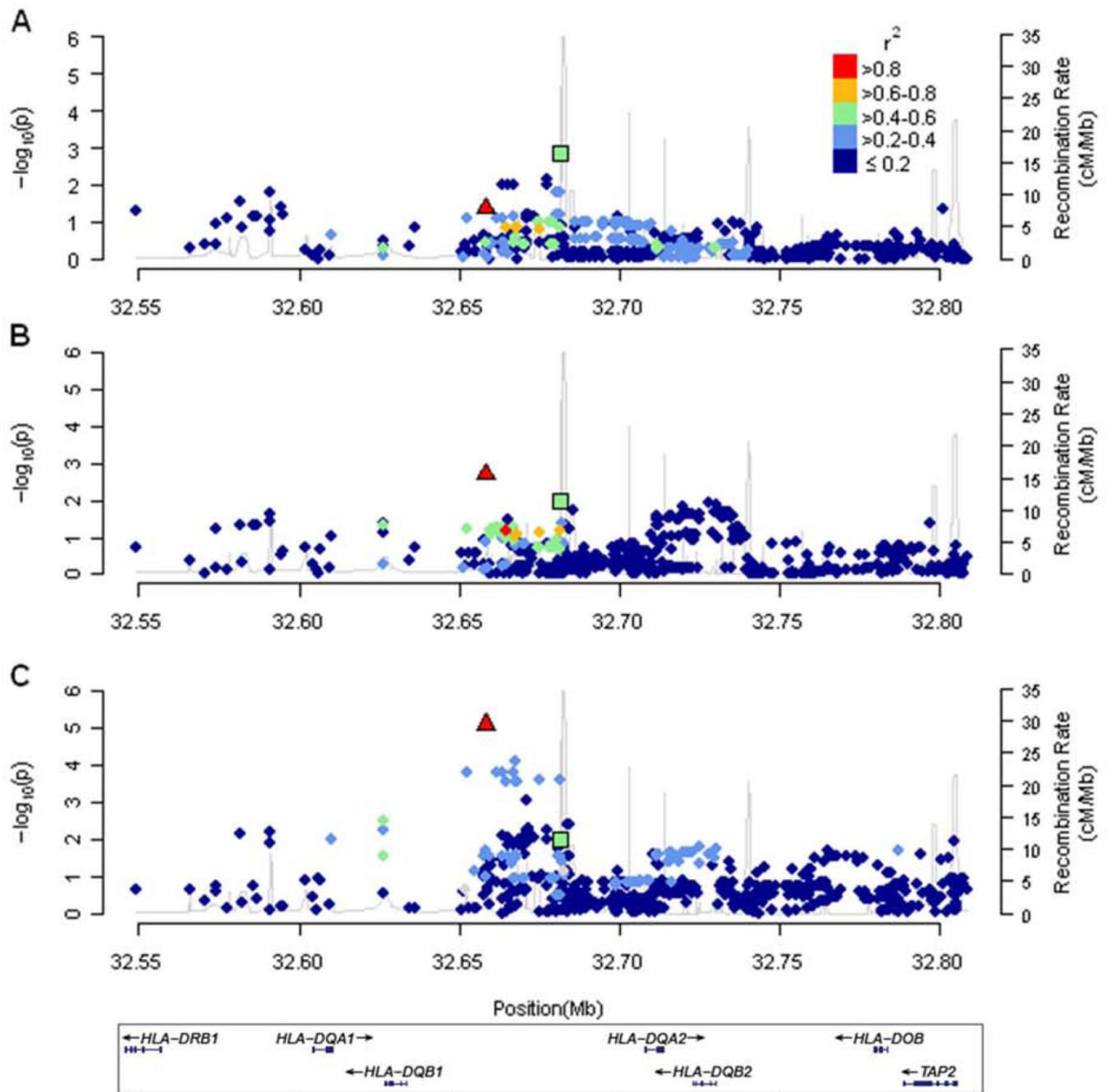
Figure 2.
Locus zoom plots of rs9469220 (triangle) located between *HLA-DQB1* and *HLA-DQA2* on chromosome 6 and its association with serum total IgE levels. The plots show the association P-values (derived from the genome wide meta-analysis) and the linkage disequilibrium (with rs9469220) in color for the surrounding single nucleotide polymorphisms in European American individuals (A), African American individuals (B), and Latino individuals (C). The polymorphism near *HLA-DQA2*, rs2858331, identified by Granada *et al*.[47] is also shown (square).

Table 1

Baseline characteristics of individuals included in the meta-analysis of IgE stratified by study.

	Study Cohort						
	SAPPHIRE (n=276)	**GRAAD-AC (n=635)**	**GRAAD-AA (n=806)**	**GALA (n=215)**	**CAMP (n=362)**	**CARE (n=229)**	**STAMPEED (n=1,769)**
Age in years – mean ± SD (range)	30.4 ± 10.5 (12–56)	28.3 ± 16.4 (3–84)	29.5 ± 18.3 (4–78)	12.9 ± 5.5 (8–35)	8.8 ± 2.1 (5–13)	6.0 ± 4.1 (1–17)	30.9 ± 14.7 (6–81)
Female – no. (%)	216 (78.3)	322 (50.7)	405 (50.2)	90 (41.9)	134 (37.0)	59 (25.8)	1,199 (67.8)
Race-ethnicity – no. (%)							
African American	276 (100)	0 (0)	806 (100)	0 (0)	0 (0)	0 (0)	752 (42.5)
African Caribbean	0 (0)	635 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
European American	0 (0)	0 (0)	0 (0)	0 (0)	362 (100)	185 (80.8)	1,017 (57.5)
Latino	0 (0)	0 (0)	0 (0)	215 (100)	0 (0)	44 (19.2)	0 (0)
History of Asthma – no. (%)	149 (54.0)	274 (43.2)	458 (56.8)	215 (100)	362 (100)	229 (100)	1,067 (60.3)
Serum total IgE (IU/ml) – geometric mean ± geometric SD	103.5 ± 4.1	188.7 ± 4.8	90.9 ± 5.0	247.2 ± 3.9	428.4 ± 4.6	34.1 ± 4.1	94.6 ± 4.8

SAPPHIRE denotes Study of Asthma Phenotypes and Pharmacogenomic Interactions by Race-ethnicity; GRAAD-AC, Genetic Research on Asthma in the African Diaspora-African Caribbean; GRAAD-AA, Genetic Research on Asthma in the African Diaspora-African American; GALA, Genetics of Asthma in Latino Americans; CAMP, Childhood Asthma Management Program; CARE, Childhood Asthma Research and Education Network; STAMPEED, SNP Typing for Association with Multiple Phenotypes from Existing Epidemiologic Data; SD, standard deviation; IgE, immunoglobulin E; and IU/ml, international units per milliliter.

STAMPEED comprises the Chicago Asthma Genetics Study (CAG), the National Heart, Lung, and Blood Institute Collaborative Studies of the Genetics of Asthma (CSGA), and the Severe Asthma Research Program (SARP).

Table 2

Genome wide meta-analysis results of the top associations with serum total IgE levels stratified by race-ethnic group. [*]

SNP	Chromosome	Position	Alleles[†]	Risk Allele[‡]	Nearest gene	P-value			
						European American (n=1,564)	African Caribbean and African American (n = 2,469)	Latino (n = 259)	All groups combined (n=4,292)
rs321588	1	96,688,818	G/A	G	PTBP2	0.0019	0.0027	0.0137	2.05×10^{-6}
rs2363709	3	67,417,105	G/A	A	SUCLG2	0.0224	1.92×10^{-5}	0.8830	3.26×10^{-6}
rs13361473	5	164,170,729	A/G	A	MAT2B	0.0001	0.0024	0.7021	2.46×10^{-6}
rs9469220	6	32,658,310	G/A	A	HLA-DQB1	0.0347	0.0017	6.43×10^{-6}	1.87×10^{-6}
rs10944017	6	85,300,836	C/T	C	TBX18	--[§]	3.42×10^{-8}	0.4222	3.88×10^{-8}
rs7751374	6	107,981,856	G/A	G	SOBP	0.0025	6.66×10^{-5}	0.0072	3.68×10^{-8}
rs10124954	9	82,836,415	T/C	T	TLE4	0.0132	3.22×10^{-5}	0.3463	1.65×10^{-6}
rs537526	11	96,840,444	G/A	A	CCDC82	0.0005	0.0004	0.5877	8.66×10^{-7}
rs6499255	16	69,830,328	A/G	A	WWP2	0.0002	0.0035	0.1177	1.03×10^{-6}
rs16977747	17	71,699,790	T/C	T	LINC00469	--[§]	2.21×10^{-6}	0.1467	7.42×10^{-7}

[*] Included the results from the following cohorts: the Study of Asthma Phenotypes and Pharmacogenomic Interactions by Race-ethnicity (SAPPHIRE), Genetic Research on Asthma in the African Diaspora-African Caribbean (GRAAD-AC), the Genetic Research on Asthma in the African Diaspora-African American (GRAAD-AA), the Genetics of Asthma in Latino Americans (GALA), Childhood Asthma Management Program (CAMP), the Childhood Asthma Research and Education Network (CARE); the Chicago Asthma Genetics Study (CAG), the National Heart, Lung, and Blood Institute Collaborative Studies of the Genetics of Asthma (CSGA), and the Severe Asthma Research Program (SARP).

[†] The first allele corresponds to the "reference/other" allele in dbSNP build 125.

[‡] The risk allele denotes the allele associated with high serum total IgE levels for all groups combined.

[§] These SNPs were uninformative based on our within group threshold requiring a minor allele frequency ≥5%.

Table 3

Characteristics of individuals included in the meta-analysis replication stratified by study.

			Study Cohort			
	SAPPHIRE* **(United States)** **(n = 1,761)**	**SAGE (United States)** **(n = 1,200)**	**GALA II** **(United States)** **(n = 1,477)**	**SAGE** **(Canada)** **(n = 423)**	**CAPPS** **(Canada)** **(n = 226)**	**Hutterites** **(United States)** **(n = 680)**
Age in years – mean ± SD (range)	34.1 ± 14.1 (12–57)	15.3 ± 5.7 (7–41)	12.8 ± 3.3 (8–21)	9.0 ± 0.5 (7–10)	7.2 ± 0.2 (6–8)	29.8 ± 16.7 (6–78)
Female – no. (%)	1,117 (63.4)	574 (47.8)	727 (49.2)	187 (44.2)	101 (44.7)	352 (51.8)
Race-ethnicity – no (%)						
African American	1,761 (100)	1,200 (100)	0 (0)	0 (0)	0 (0)	0 (0)
African Caribbean	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
European American	0 (0)	0 (0)	0 (0)	423 (100)	226 (100)	680 (100)
Latino	0 (0)	0 (0)	1,477 (100)	0 (0)	0 (0)	0 (0)
History of Asthma	1,427 (64.5)	916 (76.3)	856(58.0)	157 (37.1)	47 (20.8)	153 (22.5)
Serum total IgE (IU/ml) – geometric mean ± geometric SD	120.3 ± 4.5	119.1 ± 4.8	162.4 ± 5.0	8.3 ± 15.4	14.8 ± 14.96	23.8 ± 4.6

SAPPHIRE denotes Study of Asthma Phenotypes and Pharmacogenomic Interactions by Race-ethnicity; SAGE (United States), Study of African Americans, Asthma, Genes & Environments; GALA II, Gene-Environments and Admixture in Latino Americans; SAGE (Canada), Study of Asthma Genes and the Environment; CAPPS, Canadian Asthma Primary Prevention Study; SD, standard deviation; IgE, immunoglobulin E; and IU/ml, international units per milliliter.

*
SAPPHIRE individuals in the replication set excluded those who were part of the discovery set.

Table 4

Replication results for genome wide meta-analysis of serum total IgE levels stratified by race-ethnic group.[*]

SNP	Chromosome	Nearest gene	P-value				
			European American (n=1,329)	African Caribbean and African American (n=2,961)	Latino (n=1,477)	All groups – replication set (n=5,767)	All groups – discovery and replication set combined[†] (n=10,059)
rs321588	1	PTBP2	0.4129	0.8124	0.3737	0.9062	0.0011
rs2363709	3	SUCLG2	0.5518	0.8460	0.0093	0.1896	4.55×10^{-6}
rs13361473	5	MAT2B	0.6795	0.2455	0.6848	0.4083	0.0002
rs9469220	6	HLA-DQB1	0.0592	0.1084	0.2255	0.0074	2.45×10^{-7}
rs10944017	6	TBX18	--[‡]	0.7110	0.9087	0.8132	0.0003
rs7751374	6	SOBP	0.6858	0.5180	0.0550	0.7589	0.0006
rs10124954	9	TLE4	0.1098	0.5325	0.5034	0.5516	0.0044
rs537526	11	CCDC82	0.3519	0.6422	0.4353	0.7894	0.0022
rs6499255	16	WWP2	0.9524	0.1110	0.0308	0.0230	1.16×10^{-6}
rs16977747	17	LINC00469	--[‡]	0.0865	0.0373	0.8508	0.0031

[*] The replication set included the Study of Asthma Phenotypes and Pharmacogenomic Interactions by Race-ethnicity (SAPPHIRE) (i.e., those not in the discovery set), the Study of African Americans, Asthma, Genes & Environments (SAGE - United States), the Gene-Environments and Admixture in Latino Americans cohort (GALA 2), the Study of Asthma Genes and the Environment (SAGE - Canada); the Canadian Asthma Primary Prevention Study (CAPPS), and the Hutterites.

[†] The discovery set included the Study of Asthma Phenotypes and Pharmacogenomic Interactions by Race-ethnicity (SAPPHIRE), Genetic Research on Asthma in the African Diaspora-African Caribbean (GRAAD-AC), the Genetic Research on Asthma in the African Diaspora-African American (GRAAD-AA), the Genetics of Asthma in Latino Americans (GALA), Childhood Asthma Management Program (CAMP), the Childhood Asthma Research and Education Network (CARE); the Chicago Asthma Genetics Study (CAG), the National Heart, Lung, and Blood Institute Collaborative Studies of the Genetics of Asthma (CSGA), and the Severe Asthma Research Program (SARP).

[‡] These SNPs were uninformative based on our within group threshold requiring a minor allele frequency 5%.

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Table 5

Replication results from earlier genome wide association studies for serum total IgE levels in the current meta-analytic group stratified by race-ethnicity. [*]

Gene	SNP	Chromosome	Position	Alleles[†]	Risk Allele[‡]	P-value			
						European American (n=1,564)	African Caribbean and African American (n = 2,469)	Latino (n = 259)	All groups combined (n=4,292)
DARC	rs13962¶	1	159175527	G/A	G	0.0019	–	0.0590	0.0003
FCER1A	rs2427837§**	1	159258545	G/A	–	–	–	–	–
	rs2494264¶	1	159266838	T/A	T	0.0115	0.3614	0.1527	0.2345
	rs2251746§¶	1	159272060	T/C	T	0.0039	0.6669	0.0123	0.0072
	rs2252226∥	1	159276153	C/T	C	0.0060	0.3452	0.1306	0.0060
	rs4656784¶**	1	159326880	A/G	–	–	–	–	–
RAD50	rs2706347§	5	131905117	G/T	T	0.0121	0.0301	0.0792	0.0064
	rs3798135§	5	131965109	C/T	T	0.0127	0.0002	0.1158	8.38×10^{-5}
	rs2040704§	5	131973177	A/G	G	0.0084	0.0039	0.1076	0.0007
	rs7737470§	5	131974063	T/A	A	0.0094	0.1311	0.0929	0.0214
IL13	rs20541∥¶	5	131995964	A/G	A	0.0003	0.8945	0.5571	0.0246
	rs2243297¶**	5	131999171	T/A	–	–	–	–	–
HLA-G	rs2523809¶	6	29849619	G/T	T	0.5319	0.9972	0.2351	0.4701
HLA-A	rs2517754¶**	6	29896680	T/C	–	–	–	–	–
	rs2571391¶	6	29923838	A/C	A	0.4381	0.5206	0.5674	0.2730
HLA-DRB1	rs9271300∥**	6	32581582	C/G	–	–	–	–	–
HLA-DQA2	rs2858331¶	6	32681277	A/G	G	0.0014	0.0102	0.0099	6.30×10^{-6}
STAT6	rs167769∥¶	12	57503775	C/T	T	0.0574	8.81×10^{-5}	0.6933	2.48×10^{-5}
	rs12368672§	12	57512470	C/G	G	0.0357	0.0255	0.7028	0.0022
IL4R/IL21R	rs1859308∥	16	27397998	A/G	A	0.6262	0.1098	0.4543	0.2186

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Includes the Study of Asthma Phenotypes and Pharmacogenomic Interactions by Race-ethnicity (SAPPHIRE), the Genetic Research on Asthma in the African Diaspora-African Caribbean (GRAAD-AC) study, the Genetic Research on Asthma in the African Diaspora-African American (GRAAD-AA) study, the Genetics of Asthma in Latino Americans (GALA) study; the Childhood Asthma Management Program (CAMP), the Childhood Asthma Research and Education Network (CARE); the Chicago Asthma Genetics (CAG) study, the National Heart, Lung, and Blood Institute Collaborative Studies of the Genetics of Asthma (CSGA), and the Severe Asthma Research Program (SARP). Associations were first assessed in groups stratified by race-ethnicity, asthma status, and study before meta-analytically combining to generate the overall and population group results.

†The first allele corresponds to the "reference/other" allele in dbSNP build 125.

‡The risk allele denotes the allele associated with high serum total IgE levels for all groups combined.

§Identified by Weidinger et al.[4]

‖Identified by Moffatt et al.[6]

¶Identified by Granada et al.[47]

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Not imputed