

Cosmopolitan and ethnic-specific replication of genetic risk factors for asthma in 2 Latino populations

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Background: Although Mexicans and Puerto Ricans are jointly classified as “Hispanic/Latino,” there are significant differences in asthma prevalence, severity, and mortality between the 2 groups. We sought to examine the possibility that population-specific genetic risks contribute to this disparity.

Objectives: More than 100 candidate genes have been associated with asthma and replicated in an independent population, and 7 genome-wide association studies in asthma have been performed. We compared the pattern of replication of these associations in Puerto Ricans and Mexicans.

Methods: We genotyped Mexican and Puerto Rican trios using an Affymetrix 6.0 GeneChip and used a family-based analysis to test for genetic associations in 124 genes previously associated with asthma.

Results: We identified 32 single nucleotide polymorphism (SNPs) in 17 genes associated with asthma in at least 1 of the 2 populations. Twenty-two of these SNPs in 11 genes were significantly associated with asthma in the combined population and showed no significant heterogeneity of association, whereas 5 SNPs were associated in only 1 population and showed statistically significant heterogeneity. In a gene-based approach 2 additional genes were associated with asthma in the combined population, and 3 additional genes displayed ethnic-specific associations with heterogeneity.

Conclusions: Our results show that only a minority of genetic association studies replicate in our population of Mexican and Puerto Rican asthmatic subjects. Among SNPs that were successfully replicated, most showed no significant heterogeneity

across populations. However, we identified several population-specific genetic associations. (J Allergy Clin Immunol 2011;■■■:■■■-■■■.)

Key words: Asthma, genetics, Hispanics, Latinos, Mexicans, Puerto Ricans, replication, genome-wide association, candidate genes, effect heterogeneity

Although both Puerto Ricans and Mexicans are classified as “Hispanic/Latino,” the 2 populations have widely divergent asthma risks.¹ Puerto Ricans have the highest and Mexicans the lowest prevalence of asthma in the United States. Asthma exacerbations, hospitalizations, and mortality follow a similar pattern.² The reasons for these discrepancies are unknown and are likely related to genetic, social,³ and environmental factors, as well as their interaction.^{4,5} Although several studies have explored the epidemiology,⁶ lung function,⁷ and response to albuterol⁸ in Latino populations, we are unaware of any study that has systematically explored differences in asthma susceptibility genes between Puerto Ricans and Mexicans.

There have been more than 200 published candidate gene associations with asthma, as well as multiple reviews,^{4,11,12} candidate gene meta-analyses,¹³⁻¹⁵ and 7 genome-wide association studies (GWASs),¹⁶⁻²¹ including 1 consortium-based study that included more than 25,000 subjects of European descent recruited in 23 studies.²² Many of the initial candidate gene association studies were never replicated in an independent population, but a 2006 review by Ober and Hoffjan²³ found that 79 genes were associated with asthma in at least 2 populations. The majority of these genetic association studies of asthma have been carried out in European populations, and their relevance to Latino populations is unknown.

Although the number of comparisons used in GWASs limit their power to detect all but the strongest effect sizes,²⁴ genome-wide genotyping data can be used to examine a more limited set of associations, replicating single nucleotide polymorphism (SNPs) or genes previously associated with a disease or phenotype.²⁵ Such analyses demonstrate that although a minority of genetic associations identified before the availability of genome-wide genotyping are replicated using GWAS data, those that can be conclusively replicated have substantial genetic effects. Two asthma studies have formally examined candidate genes using genome-wide data.^{26,27} In each study only a minority of the evaluated genes were associated with asthma. Only an association between dipeptidyl peptidase 10 (*DPP10*) and asthma was replicated in both studies.

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Supported by the National Institutes of Health (2T32GM007546, 1RC2 HL101651, ES015794, U19 AI077439, HL088133, and HL078885) and the Flight Attendant Medical Research Institute (FAMRI).

Disclosure of potential conflict of interest: J. M. Galanter receives research support from the National Institutes of Health. C. R. Gignoux owns stock in 23andMe, Inc. The rest of the authors have declared that they have no conflict of interest.

Received for publication November 17, 2010; revised February 26, 2011; accepted for publication March 31, 2011.

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0091-6749/\$36.00

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doi:10.1016/j.jaci.2011.03.050

Abbreviations used

GALA: Genetics of Asthma in Latino Americans
 GWAS: Genome-wide association study
 OR: Odds ratio
 SNP: Single nucleotide polymorphism

In this study we performed a literature search to identify genes that had previously been associated with asthma in a GWAS or at least 2 candidate gene studies. We used genome-wide data to test whether asthma-associated SNPs in those genes are associated with asthma in 2 populations of Latino asthmatic subjects enrolled in the Genetics of Asthma in Latino Americans (GALA) study.²⁸ To test for the possibility that different variants within those genes are associated with asthma, we also performed a gene-based study, testing all genotyped SNPs in or near the genes and adjusting for multiple comparisons using a gene-based permutation approach. The process of SNP and gene selection is summarized in Fig 1. Because the study includes subjects of both Mexican and Puerto Rican descent, we sought to identify genes that confer risk in both populations, as well as genes that confer ethnic-specific risk.

METHODS**Subjects**

Mexican and Puerto Rican probands with asthma, aged 8 to 40 years, and their biological parents were recruited for the GALA study.²⁸ Puerto Rican probands were recruited from Puerto Rico and New York City, and Mexican probands were recruited in Mexico City and the San Francisco Bay Area. Probands were invited to participate if they had a physician's diagnosis of asthma and were either taking a medication for asthma or had 2 or more asthma-related symptoms (wheezing, coughing, and/or dyspnea) in the preceding year. Participants were included if their self-identified ethnicity was Mexican or Puerto Rican and if all 4 of their biological grandparents were of the same Latino ethnicity. Detailed recruitment criteria and participants' characteristics are described elsewhere and in the **Methods** section of this article's Online Repository at www.jacionline.org.^{8,28} Local institutional review boards approved all the studies. All adult subjects provided informed consent. In the case of minors, subjects provided age-appropriate assent and their parents provided informed consent.

Genotyping

Genotyping was performed on the Affymetrix 6.0 GeneChip Array (Affymetrix, Santa Clara, Calif), which contains more than 900,000 SNPs before quality control measures. Markers were included based on 95% call rates, Hardy-Weinberg equilibrium *P* values of greater than 10^{-5} , and less than 5 heterozygous genotype calls in male subjects for X-linked markers. We filtered out SNPs with ambiguous mappings in the hg18 annotation track and those with high inconsistency in allele calling between plates. Subjects were excluded if they had less than a 95% call rate, unexpected cryptic relatedness, or Mendelian inconsistencies.

SNP-based replication

Fig 1 summarizes the procedure used to select SNPs. Genes were included if they were associated with asthma in a GWAS or at least 2 candidate gene studies. A further description of the criteria and search strategy used to identify genes for replication is available in the **Methods** section of this article's Online Repository.

We used the program BEAGLE version 3.2²⁹ to phase and impute genotypes of 3.5 million SNPs. We used the combined consensus set of phased haplotypes in Release 21 of HapMap Phase II using Yorubans, Centre d'Etude du

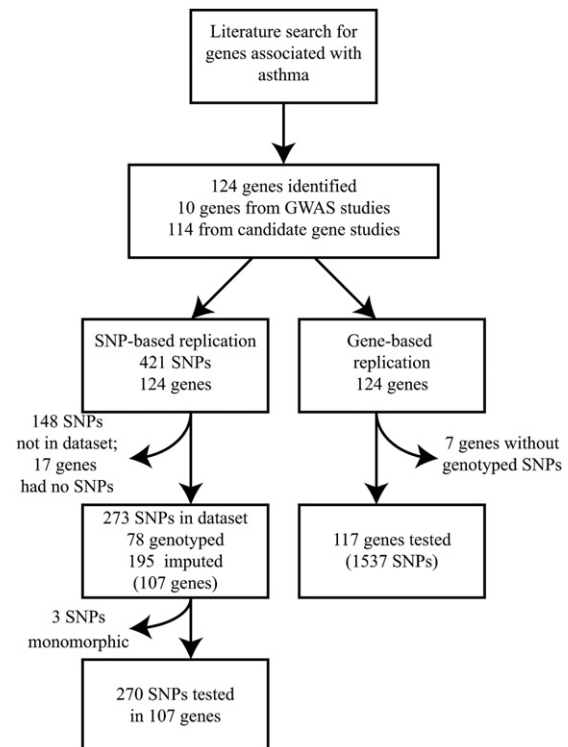


FIG 1. SNP and gene selection process.

Polymorphisme Humain Européens, and the combined Chinese and Japanese populations as reference populations.³⁰ We tested all SNPs previously implicated in asthma within the identified genes using the transmission disequilibrium test, as implemented in the program PLINK version 1.07,³¹ in the combined population and separately in Puerto Ricans and Mexicans. We tested whether the effect magnitude (odds ratio [OR]) between Mexicans and Puerto Ricans was homogenous or heterogeneous by comparing the ratio of transmitted and untransmitted alleles using a χ^2 test with 3 *df*, where the null hypothesis states that there is no difference between the ORs in Mexicans and Puerto Ricans (ie, the effect is homogenous). Homogeneity in the minor allele frequency of Mexican and Puerto Rican parents was compared by using a χ^2 test.

Gene-based replication

Given the possibility of a failure to replicate an association because of differing linkage disequilibrium patterns between the GALA populations and those in which the association was first reported, we supplemented our analysis by performing a "gene-based" replication. For every gene identified above, we tested all genotyped SNPs within 1 kb of the transcription start and stop sites of RefSeq genes (release 43).³² Because the gene was the unit of replication, we corrected the results for the number of comparisons made within each gene using a permutation procedure. We performed 10,000 gene-dropping permutations, whereby the transmitted allele was permuted with a 50:50 probability while maintaining linkage disequilibrium between SNPs. Each observed test statistic was compared against the maximum of all permuted statistics (ie, over all SNPs in the gene) to control for the gene-wide error rate.³¹

RESULTS**Subjects**

Demographic, clinical, and spirometric characteristics of all asthmatic probands who enrolled in this study are shown in Table I. There were a total of 509 subjects with complete

TABLE I. Demographic and baseline characteristics for the GALA probands

	Puerto Ricans	Mexicans	<i>P</i> value for difference
No.	373 (241 from PR, 132 from NY)	300 (99 from MX, 201 from SF)	
Age (y)	11.9 (10-15)	13.2 (11-20)	<.001
Sex (% male)	55.5	55.2	.8
BMI (kg/m ²)	21.3 (17-26)	23.8 (20-28)	<.001
Serum total IgE (IU/mL)	262 (96-618)	249 (94-599)	.7
Severity (% severe)	66.9	67.0	.3
Spirometry (no. with full data)	363	273	
Pre-FEV ₁ (% predicted)	84 (74-93)	89 (77-100)	<.001
FVC (% predicted)	93.8 (83-105)	97.8 (87-109)	.2
FEV ₁ /FVC (%)	79.0 (72-85)	80.7 (75-86)	.007
ΔFEV ₁ (relative %)	4.9 (0.6-10)	7.4 (4-14)	<.001

For continuous variables, the median and interquartile range are displayed, and differences between the 2 populations were tested with a *t* test. A χ^2 test was used to test for differences in proportions.

BMI, Body mass index; ΔFEV₁, change in FEV₁ after the administration of albuterol; FVC, forced vital capacity; MX, Mexico City; NY, New York; PR, Puerto Rico; SF, San Francisco.

spirometric data (Mexican, *n* = 273; Puerto Rican, *n* = 336). The median age of the Mexican and Puerto Rican subjects with asthma was 13 and 12 years, respectively.

A box plot of ancestry estimates for the Puerto Rican and Mexican probands is shown in Fig 2. A multidimensional scaling plot of the 2 populations can be found in Fig E1 in this article's Online Repository at www.jacionline.org. Overall, Mexicans had 39% (95% CI, 37% to 41%; *P* < .0001) higher Native American ancestry than Puerto Ricans, whereas Puerto Ricans had 25% (95% CI, 23% to 27%; *P* < .0001) higher European ancestry than Mexicans.

Gene selection

We identified 124 candidate genes for analysis based on a search of asthma and related phenotypes conducted in September 2010. Of these, 10 genes were initially identified in a GWAS, and 114 were found to be associated with asthma in at least 2 independent candidate gene studies (Fig 1). Within these genes, 418 SNPs were identified as having been associated with asthma in at least 1 study. Two hundred seventy-three SNPs were genotyped (*n* = 78) or imputed (*n* = 195) in our sample population; the remaining SNPs were not among the 3.5 million SNPs in the HapMap II reference populations. Seventeen genes had no asthma-associated SNPs genotyped or imputed for analysis. Three SNPs were monomorphic in our population, leaving 270 for analysis. In the gene-based replication study, we identified 1537 genotyped SNPs that were within 1 kb of 117 genes; 7 of the 124 genes selected for analysis had no genotyped SNPs that met the criteria for analysis.

SNP-based replication

Fig 3 shows the significant results of the SNP-based replication for asthma. The significant and full results of the SNP-based replication can be found in Tables E1 and E2 in this article's Online Repository at www.jacionline.org. A QQ-plot comparing

observed versus expected *P* values in the Puerto Rican, Mexican, and combined samples can be found in Fig E2 in this article's Online Repository at www.jacionline.org and shows an excess of low *P* values. *P* values were lower in the combined sample than in each of the individual samples, which is consistent with the combined sample's larger sample size and greater power.

Of the 270 genotyped or imputed SNPs in the 107 genes analyzed, 32 SNPs in 17 genes were associated with asthma in at least 1 of the 2 populations (*P* < .05). In the combined population 22 SNPs in 11 genes were associated with asthma in the combined population and did not display significant heterogeneity between Mexicans and Puerto Ricans (*P*_{heterogeneity} > .1). The most significant association was rs1342326 in the *IL33* gene, the C allele (minor allele) of which was found to confer a risk for asthma with an OR of 1.65 (95% CI, 1.29-2.11; *P* = 6×10^{-5}) in the combined population. In all but 1 SNP, rs2069762 in *IL2* (see Table E1), there was a statistically significant difference in the minor allele frequency between Mexicans and Puerto Ricans, ranging from 4.4% to 18.8%, which is consistent with the differences in ancestry between the 2 groups (Fig 2).

Five genes had SNPs that displayed significant effect heterogeneity between the 2 groups (*P*_{heterogeneity} < .1) and were associated with asthma in only 1 of the 2 populations (*P* < .05), including 3 associated with Mexicans but not with Puerto Ricans (Fig 3, B, and Table E1). These include an SNP in ORM1-like protein 3 (*ORMDL3*), rs4795408, which showed an OR of 1.55 (95% CI, 1.18-2.03; *P* = .001) in Mexicans but an OR of 0.98 (95% CI, 0.76-1.25; *P* = .8) in Puerto Ricans and a *P* value for heterogeneity of .02. This SNP was in partial linkage disequilibrium with SNP rs8076131, the second most strongly associated SNP in the combined population (Fig 3, A, and see Table E1) and in both ethnic groups. However, linkage between rs4795408 and rs8076131 was substantially stronger in Mexicans (*r*² = 0.46) than in Puerto Ricans (*r*² = 0.26), as shown in Fig E3 in this article's Online Repository at www.jacionline.org. Two genes, α1B-adrenergic receptor (*ADRA1B*) and nucleotide-binding oligomerization domain protein 1 (*NOD1*), had SNPs associated with asthma in Puerto Ricans but not Mexicans and had significant effect heterogeneity at a *P* value of less than .1. A Venn diagram summarizing the replication pattern of the genes analyzed is shown in Fig 4.

Gene-based replication

Among the 124 genes evaluated for replication, we found at least 1 SNP to test for association in 117 genes. Within these, 148 SNPs in 45 genes were nominally associated with asthma in at least 1 of the 2 populations, and 78 SNPs were nominally associated with asthma in the combined population. After adjusting for multiple comparisons with permutation testing, 16 SNPs in 11 genes were associated with asthma in at least 1 population. Table E3 in this article's Online Repository at www.jacionline.org shows the 6 genes associated with asthma in the combined population without effect heterogeneity and the 5 genes associated with asthma in 1 of the 2 populations with significant heterogeneity.

Three genes with effect heterogeneity were associated with asthma in Mexicans but not Puerto Ricans, including nucleopeptide S receptor 1 (*NPSR1*) (OR in Mexicans, 2.00; 95% CI, 1.29-3.1; *P*_{permuted} = .045; *P*_{heterogeneity} = .02), membrane-spanning 4 domains, subfamily A, member 2 (*MS4A2*) (OR in Mexicans,

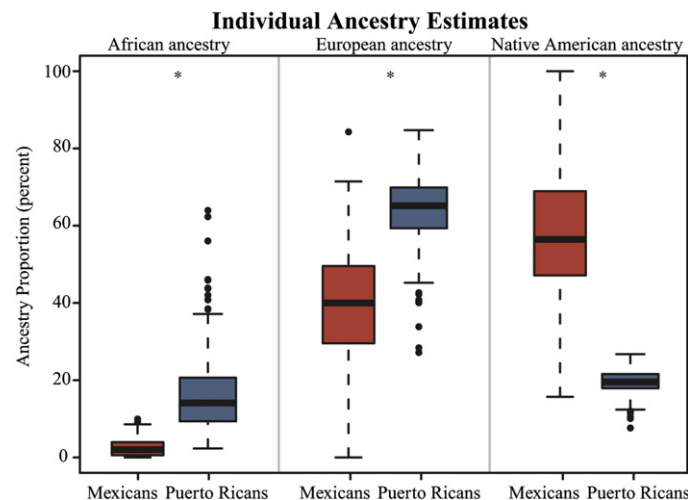


FIG 2. Box plot of individual ancestry estimates of GALA Mexican and Puerto Rican subjects. On average, Puerto Ricans have higher African and European ancestry than Mexicans, whereas Mexicans have higher Native American ancestry. *Significant difference between the groups.

0.65; 95% CI, 0.47-0.90; $P_{\text{permuted}} = .008$, $P_{\text{heterogeneity}} = .01$), and *ADRA1B* (OR in Mexicans, 2.50; 95% CI, 1.28-4.88; $P_{\text{permuted}} = .048$; $P_{\text{heterogeneity}} = .02$; see Table E2). In this analysis the SNP in *ADRA1B* associated with asthma (rs6884129) was different than the one associated with asthma in Puerto Ricans in the SNP-based association (rs10515802). These 2 SNPs in *ADRA1B* are not in linkage disequilibrium in either of the 2 populations ($r^2 = 0.01$ in Puerto Ricans, $r^2 = 0$ in Mexicans). Two genes, histamine n-Methyltransferase (*HNMT*) (OR in Puerto Ricans, 0.66; 95% CI, 0.48 - 0.90; $P_{\text{permuted}} = .03$, $P_{\text{heterogeneity}} = .06$) and nitric oxide synthase (*NOS3*) (OR in Puerto Ricans, 0.48; 95% CI, 0.33-0.71; $P_{\text{permuted}} = .0007$; $P_{\text{heterogeneity}} = .053$), were associated with asthma in Puerto Ricans but not Mexicans.

In the combined analysis 11 SNPs in 6 genes were associated with asthma and had no significant effect heterogeneity (see Table E3). Only 2 of the 6 genes that showed gene-based replication, Major Histocompatibility Complex, Class II, DQB1 (*HLA-DQB1*) (combined OR, 0.75; 95% CI, 0.60-0.94; $P = .01$) and *IL16* (combined OR, 1.34; 95% CI, 1.11-1.61; $P = .002$), did not have SNPs associated with asthma in the SNP-based replication.

DISCUSSION

In this study we performed a literature search and identified 124 genes that were previously associated with asthma in a GWAS or 2 independent candidate gene studies and tested their association in 2 Latino populations. Our SNP-level replication found that 38 SNPs in 17 genes were associated with asthma in at least 1 population, whereas an additional 4 genes were associated with at least 1 population in the gene-based study. The pattern of replication of these genes falls into several categories, as shown in Fig 4.

SNPs in 3 of the genes, *ORMDL3*, *GSDMB*, and *IL33*, replicate in both populations and generally had no significant effect heterogeneity between the 2 Latino populations. These 3 genes represent the most confident replications. Interestingly, all 3 of these genes were identified in GWASs, and all 3 are associated with asthma in the large Multidisciplinary Study to Identify the Genetic and Environmental Causes of Asthma in the European Community (GABRIEL consortium) study.²² It is not surprising that

the 2 genes in the 17q21 locus (*ORMDL3* and *GSDMB*) replicate in our population because we had previously been able to replicate the association in these 2 Latino populations in GALA, as well as in an African American population.³³

Several genes were associated with asthma in only 1 of the 2 populations, and did not show substantial heterogeneity of effect or association in the combined population. It is difficult to interpret the meaning of these findings because they could represent spurious associations. However, they could also represent cases of ethnic-specific replication for which the test of heterogeneity was underpowered to detect differences between the 2 ethnic groups. For example, SNP rs17576 showed an association in Puerto Ricans (OR, 1.34) but not Mexicans (OR, 0.96). However, the test for heterogeneity failed to reject the null hypothesis ($P_{\text{heterogeneity}} = .2$). It is possible that the test for heterogeneity would have been significant in a larger sample. However, because the 95% CI for the OR for Mexicans was broad (0.71-1.31), an effect magnitude comparable to that seen in Puerto Ricans is also possible.

A third category contains genes associated with asthma in the combined population, without significant heterogeneity between the populations. In some cases, although the effect magnitude was similar and in the same direction in the 2 populations, the association did not reach statistical significance in at least 1 of the 2 groups. This might be the result of loss of power from dividing into subgroups by ethnicity.

Finally, there are several genes that show an ethnic-specific replication pattern. Specifically, SNPs on genes *NOD1*, *HNMT*, and *NOS3* in Puerto Ricans and *NPSR1* and *MS4A2* in Mexicans were associated with asthma in one Latino ethnicity but not the other, and there was substantial heterogeneity between the 2 populations. SNPs in 2 other genes, *ORMDL3* and *ADRA1B*, also showed this pattern. In the case of *ORMDL3*, other SNPs in this gene in partial linkage disequilibrium showed a robust association in both populations, whereas in the case of *ADRA1B*, different unlinked SNPs in the gene were associated with asthma separately in each population.

Several factors could explain this ethnic-specific heterogeneity of effect. The first and most likely is that SNPs of interest

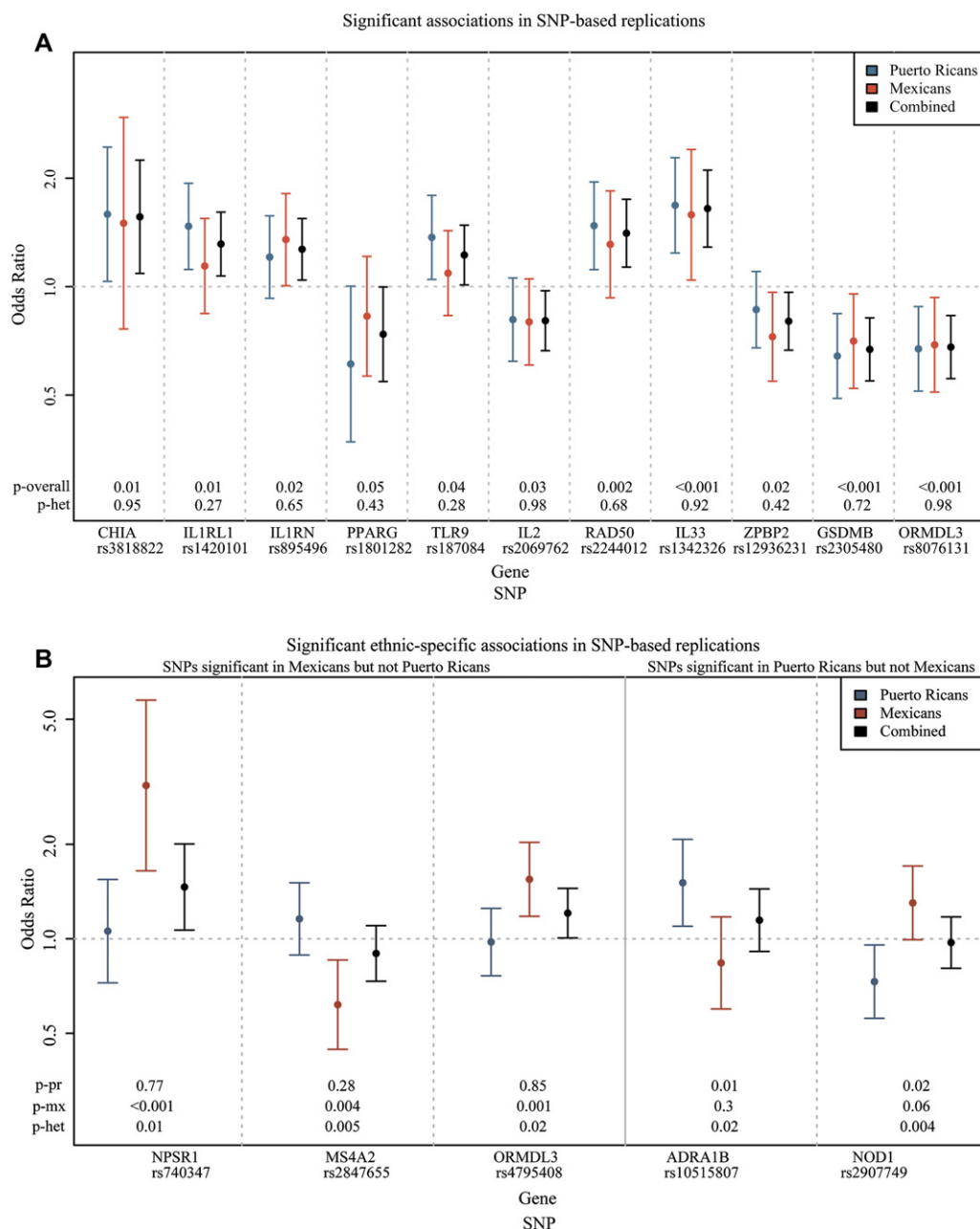
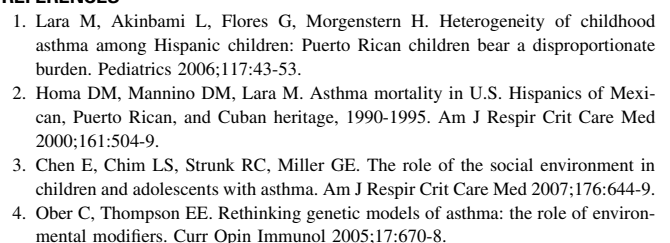


FIG 3. SNP-based replication showing ORs (95% CI) for Mexican, Puerto Rican, and combined samples. The top graph shows the genes that replicated in the combined population with low heterogeneity, and the bottom graph shows genes that replicated in one population and had significant heterogeneity.

might be indirectly tagging underlying causal variants. Differing patterns of linkage disequilibrium between the underlying causal variant or variants and the genotyped SNPs in Puerto Ricans and Mexicans contribute significantly to observed effect heterogeneity. Bryc et al¹⁰ found that Mexicans have a larger degree of linkage disequilibrium (r^2) as a function of physical distance on the chromosome than Puerto Ricans. This is due to the greater proportion of Native American ancestry in Mexicans and African ancestry in Puerto Ricans; Native Americans have higher linkage disequilibrium as a function of physical distance than Africans. In the case of *ORMDL3*, in which several SNPs were strongly associated with asthma in both populations, greater linkage disequilibrium in Mexicans

than Puerto Ricans likely explains the association of SNP rs4795408 with asthma in the former group but not the latter (see Fig E2).

Second, although the common disease, common variant hypothesis suggests that multiple common older variants that predated population divergence confer relatively small risks individually but jointly contribute to asthma susceptibility, recent work has suggested that rare variants that arose more recently with stronger effects might be responsible for common diseases.³⁴ Because rare variants might have arisen after populations diverged, they are more likely to be population specific. These rare variants might be overrepresented in specific ethnic groups.³⁵ Thus the presence of undetected rare causal variants in only one of



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METHODS

Subject recruitment

Trained interviewers administered a modified version of the 1978 American Thoracic Society–Division of Lung Diseases Epidemiology Questionnaire^{E1} to all probands or the parents of minors. Blood samples were collected from each participant, and DNA was extracted and purified, deidentified, and stored at the University of California, San Francisco, DNA Bank.

Determination of genetic ancestry

We implemented a 3-population model to estimate individual ancestry proportions using the program ADMIXTURE.^{E2} We filtered our genome-wide markers to eliminate markers in linkage equilibrium at an r^2 value of less than 0.1. Genotypes from ancestral populations, including HapMap African (Yoruban and Luhya) and European (Centre d'Etude du Polymorphisme Humain and Tuscan) populations,^{E3} a population of Mayan and Nahuatl Native Americans from Mexico and Quechuan, and Aymaran Native Americans from the Andes (courtesy of Mark Shriver),^{E4} define the ancestral clusters relevant to Hispanics/Latinos. Multidimensional scaling of the GALA subjects was performed by generating a pairwise identity-by-state distance matrix and extracting principal coordinates with the program PLINK.^{E5} The first 2 principal coordinates were then plotted to show the relative positions of the GALA subjects and populations representing the ancestral persons.

Selection of candidate genes and SNPs for replication

We identified studies by searching the National Institutes of Health's Genetic Association Database^{E6} using "asthma" as the broad disease phenotype. We also searched the Human Genetic Epidemiology (HuGE) database^{E7} for "asthma," "bronchial hyperreactivity," and "status asthmaticus." We supplemented this search by identifying review articles on asthma genetics, as well as articles using GWAS data to test candidate genes in asthma. For each gene identified, we performed a PubMed search of the gene name (and all alternate names) and "asthma" or "bronchial hyperreactivity" to identify all published articles relating to the gene. We included genes for analysis if they were

identified in a GWAS or if they were found to be associated with asthma or related traits (eg, bronchial hyperreactivity) in at least 2 independent studies or at least 1 meta-analysis, regardless of the population.

Determination of site-specific effect heterogeneity

To test whether the observed heterogeneity was due to gene-environment interactions, we evaluated the proportion of between-site heterogeneity that was attributable to differences in effect between ethnicity. We used the R-package metafor^{E8} to perform a mixed-effects meta-analysis with a DerSimonian-Laird estimator of heterogeneity to combine data from the 4 sites by using ethnicity as a grouping variable. This produces an estimate, τ representing the magnitude of the between-site heterogeneity, a P value for the test of homogeneity between sites, a P value for the test of homogeneity between ethnicities in the context of heterogeneity between sites, and a residual τ value, representing the residual amount of heterogeneity between sites once we have accounted for the heterogeneity between ethnicities.

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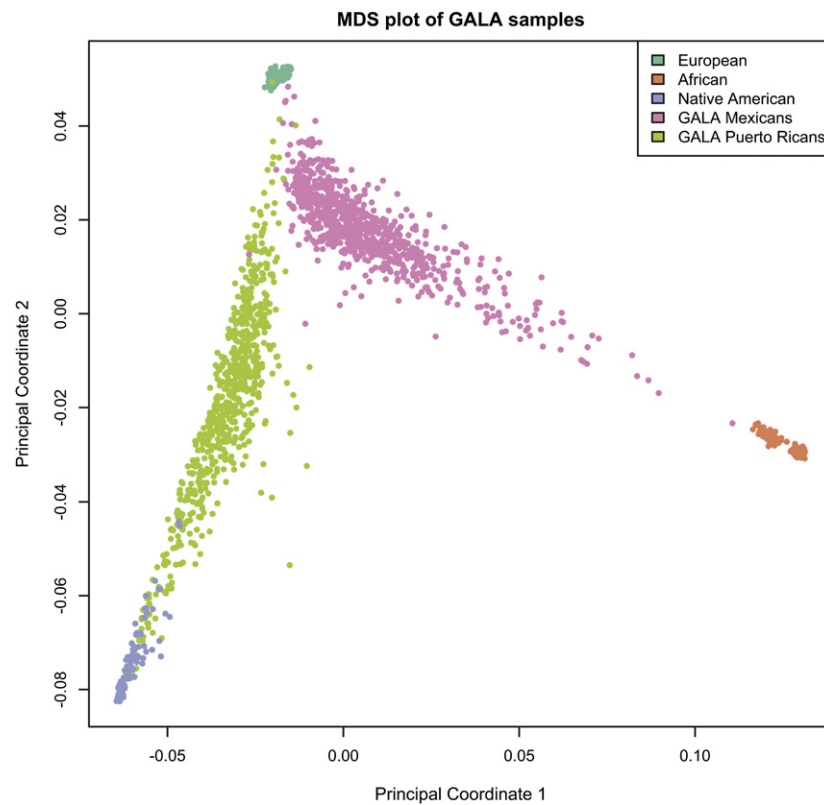


FIG E1. Multidimensional scaling plot of the first 2 principal coordinates for GALA Puerto Rican and Mexican subjects. HapMap 3 European and African subjects and 4 populations of Native Americans are shown for comparison. Generally, Mexicans align on the axis between Europeans and Native Americans, whereas Puerto Ricans align in the axis between Europeans and Africans.

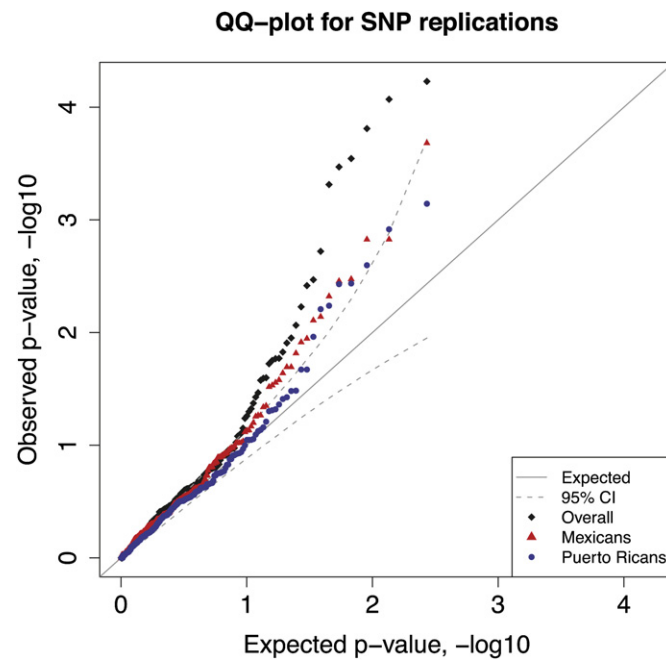


FIG E2. QQ-plot of the SNP-based replication comparing observed versus expected *P* values in Puerto Ricans, Mexicans, and the combined population.

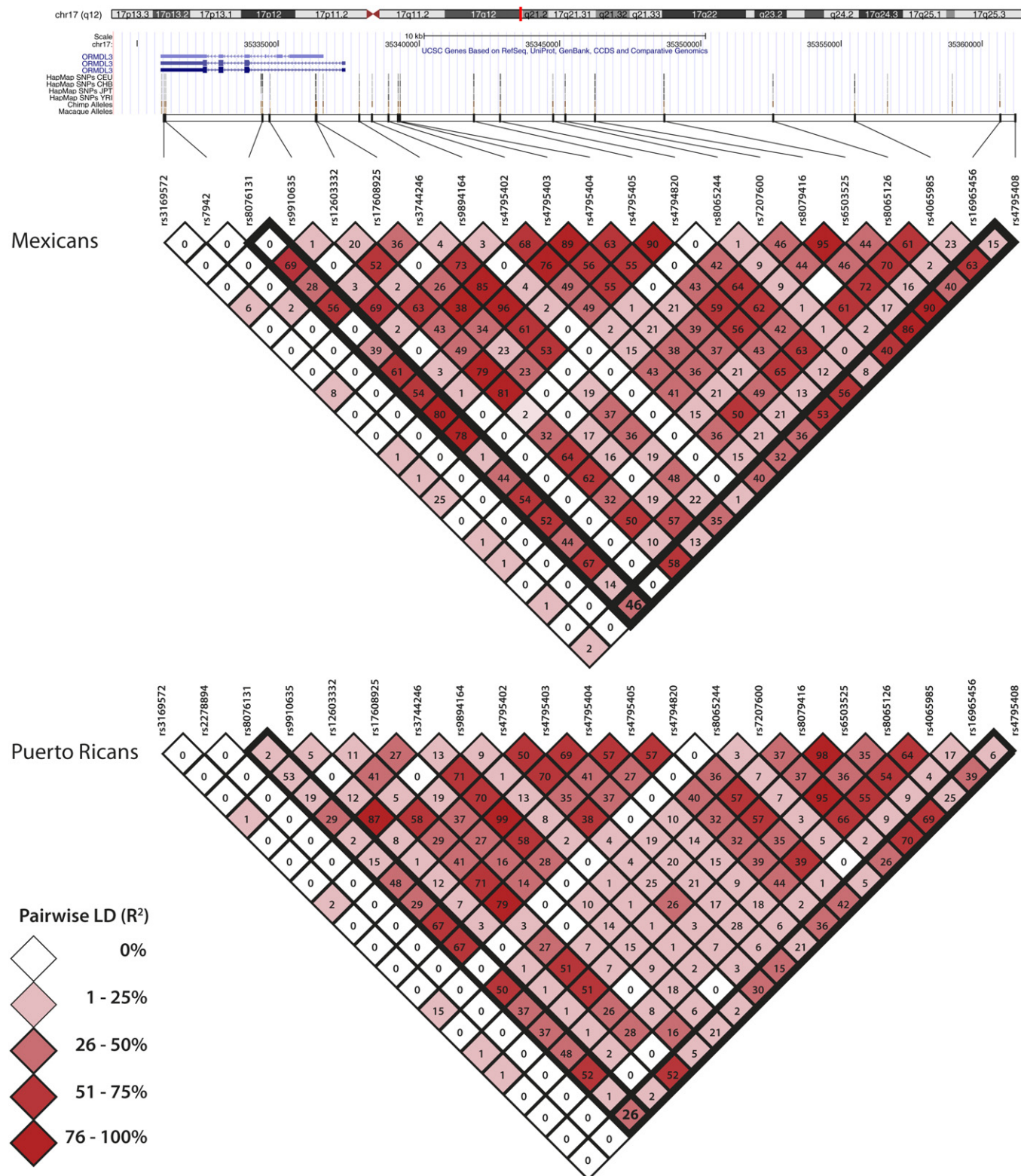


FIG E3. Genetic structure and linkage map of *ORMDL3*, a gene with strong associations in both Mexicans (top) and Puerto Ricans (bottom). SNP rs8076131 (left bold box) showed the strongest association in the combined sample and a significant association in each population. SNP rs4795408 (right bold box) showed a significant association in Mexicans but not Puerto Ricans.

TABLE E1. Significant results of SNP-based replication reported by gene

Gene	SNP rsID	Chromosome	OR	95% CI	P (overall)	OR (MX)	OR (PR)	P (het)	MAF (MX)	MAF (PR)	P (freq)
A. SNPs associated in overall population showing no significant effect heterogeneity											
<i>CHIA</i>	rs3818822	1	1.56	1.09-2.25	.01	1.50	1.59	.9	0.04	0.10	<.0001
<i>IL1RL1</i>	rs1420101	2	1.31	1.07-1.61	.01	1.14	1.47	.3	0.25	0.30	.03
<i>IL1RN</i>	rs895496	2	1.27	1.04-1.55	.02	1.35	1.21	.7	0.28	0.37	<.0001
<i>PPARG</i>	rs1801282	3	0.74	0.55-1.00	.05	0.83	0.61	.4	0.13	0.07	<.0001
<i>TLR9</i>	rs187084	3	1.22	1.01-1.48	.04	1.09	1.37	.3	0.43	0.31	<.0001
<i>IL2</i>	rs2069762	4	0.80	0.66-0.97	.03	0.80	0.81	1.0	0.31	0.29	.6
<i>RAD50</i>	rs2244012	5	1.41	1.13-1.75	.002	1.31	1.48	.7	0.21	0.26	.003
<i>IL33</i>	rs1342326	9	1.65	1.29-2.11	6×10^{-5}	1.58	1.68	.9	0.11	0.22	<.0001
<i>ZBP2</i>	rs12936231	17	0.80	0.67-0.96	.02	0.73	0.86	.4	0.31	0.45	<.0001
<i>GSDMB</i>	rs2305479	17	0.70	0.58-0.85	.0003	0.74	0.67	.7	0.29	0.35	.002
<i>ORMDL3</i>	rs8076131	17	0.68	0.56-0.83	.0002	0.69	0.67	1.0	0.25	0.35	<.0001
B. SNPs associated in one population showing significant effect heterogeneity											
<i>ADRA1B</i>	rs10515807	5	1.15	0.91-1.44	.2	0.84	1.51*	.02	0.19	0.18	.6
<i>NPSR1</i>	rs740347	7	1.46	1.07-2.00	.02	3.08*	1.06	.006	0.06	0.11	.0002
<i>NOD1</i>	rs2907749	7	0.97	0.81-1.17	.8	1.30	0.73*	.004	0.33	0.29	.03
<i>MS4A2</i>	rs2847655	11	0.90	0.73-1.10	.3	0.62*	1.16	.005	0.23	0.33	<.0001
<i>ORMDL3</i>	rs4795408	17	1.21	1.01-1.45	.04	1.55*	0.98	.02	0.63	0.38	<.0001
C. SNPs associated in one population that do not show significant effect heterogeneity											
<i>C5</i>	rs17611	9	1.19	1.00-1.41	.05	1.10	1.28*	.4	0.49	0.41	.0002
<i>NQO1</i>	rs1800566	16	1.10	0.98-1.44	.08	1.07	1.31*	.4	0.37	0.27	<.0001
<i>MMP9</i>	rs17576	20	1.16	0.94-1.42	.2	0.96	1.34*	.2	0.26	0.28	.01

Only the SNP with the smallest association *P* value within each gene is included in the table.

MX, Mexicans; *P* (*freq*), *P* value for heterogeneity in minor allele frequency; *P* (*het*), *P* value for heterogeneity of effect, *PR*, Puerto Ricans, *MAF*, minor allele frequency.

*Population in which there is a significant association (*P* < .05).

TABLE E2. Results of SNP-based replication

Gene	SNP rsID	Chromosome	Position	A1	A2	Overall OR (95% CI)	P (overall)	OR (Mex)	P (Mex)	OR (PR)	P (PR)	P (het)	P (freq)
<i>MTHFR</i>	rs1801133	1	11790644	A	G	1.09 (0.91-1.30)	.367	1.07	.604	1.10	.452	.951	<.001
<i>NPPA</i>	rs5067	1	11840247	G	A	1.00 (0.78-1.29)	1.000	0.85	.491	1.08	.639	.488	<.001
<i>NPPA</i>	rs5065	1	11840334	G	A	1.00 (0.78-1.29)	1.000	0.85	.491	1.08	.639	.488	<.001
<i>NPPA</i>	rs5063	1	11841914	T	C	0.98 (0.64-1.49)	.915	0.95	.876	1.00	1.000	.919	.982
<i>CHIA</i>	rs3806448	1	111544247	G	A	0.98 (0.81-1.19)	.847	1.11	.496	0.90	.416	.345	<.001
<i>CHIA</i>	rs3818822	1	111569250	A	G	1.56 (1.09-2.25)	.015	1.50	.237	1.59	.033	.948	<.001
<i>CHIA</i>	rs2282290	1	111575493	G	A	0.93 (0.76-1.14)	.470	0.80	.157	1.04	.785	.253	<.001
<i>DENND1B</i>	rs2786098	1	194057565	T	G	1.02 (0.80-1.29)	.902	1.13	.521	0.93	.680	.529	.764
<i>DENND1B</i>	rs2821106	1	194115942	T	C	0.92 (0.64-1.32)	.644	1.20	.547	0.78	.292	.351	.066
<i>DENND1B</i>	rs12134409	1	194123724	T	C	0.91 (0.72-1.15)	.440	0.91	.564	0.92	.607	.929	<.001
<i>DENND1B</i>	rs2111931	1	194260875	C	T	0.91 (0.73-1.13)	.373	0.88	.417	0.93	.645	.872	.050
<i>DENND1B</i>	rs10737692	1	194280590	A	G	0.94 (0.76-1.17)	.585	0.96	.811	0.92	.601	.941	.354
<i>DENND1B</i>	rs12127378	1	194332749	C	T	0.87 (0.69-1.10)	.243	0.88	.414	0.87	.405	.926	.003
<i>DENND1B</i>	rs12041661	1	194333325	A	C	0.87 (0.69-1.10)	.243	0.88	.414	0.87	.405	.926	.003
<i>DENND1B</i>	rs10442656	1	194338365	T	C	0.90 (0.72-1.13)	.368	0.88	.417	0.93	.639	.883	.053
<i>DENND1B</i>	rs2477070	1	194344416	G	A	0.87 (0.69-1.10)	.240	0.87	.411	0.87	.401	.926	.002
<i>DENND1B</i>	rs1747827	1	194347048	T	C	0.88 (0.70-1.11)	.265	0.89	.461	0.87	.401	.975	.002
<i>DENND1B</i>	rs2488411	1	194390456	C	T	0.88 (0.71-1.09)	.246	0.84	.265	0.92	.590	.752	.090
<i>DENND1B</i>	rs1891497	1	194391212	A	G	0.88 (0.70-1.11)	.267	0.90	.514	0.86	.358	.932	.002
<i>DENND1B</i>	rs1747815	1	194429760	T	C	0.89 (0.71-1.13)	.344	0.91	.564	0.88	.445	.979	<.001
<i>DENND1B</i>	rs1775454	1	194458955	T	C	0.90 (0.72-1.14)	.381	0.89	.496	0.91	.574	.994	.313
<i>DENND1B</i>	rs1775456	1	194464712	G	A	0.90 (0.71-1.15)	.389	0.93	.669	0.87	.425	.876	<.001
<i>DENND1B</i>	rs1924518	1	194469984	A	G	0.90 (0.71-1.15)	.389	0.93	.669	0.87	.425	.876	<.001
<i>DENND1B</i>	rs1775444	1	194472347	T	C	0.90 (0.71-1.15)	.389	0.93	.669	0.87	.425	.876	<.001
<i>DENND1B</i>	rs12026183	1	194544689	T	C	0.87 (0.65-1.16)	.334	1.04	.837	0.71	.108	.248	.020
<i>DENND1B</i>	rs10922300	1	194546342	T	C	0.98 (0.65-1.48)	.917	1.19	.612	0.87	.593	.607	.074
<i>DENND1B</i>	rs10922326	1	194599319	G	T	1.03 (0.77-1.38)	.824	1.10	.670	0.98	.917	.819	.288
<i>CHI3L1</i>	rs4950928	1	199887539	G	C	0.87 (0.69-1.10)	.250	0.83	.331	0.90	.486	.840	<.001
<i>CHI3L1</i>	rs4950929	1	199891783	G	T	0.88 (0.67-1.15)	.339	0.98	.917	0.81	.237	.572	.046
<i>CHI3L1</i>	rs946263	1	199897038	G	A	0.97 (0.72-1.30)	.823	1.29	.317	0.83	.305	.208	<.001
<i>CHI3L1</i>	rs2153101	1	199900131	A	T	0.90 (0.69-1.18)	.451	0.98	.917	0.85	.361	.698	.070
<i>IL10</i>	rs1800871	1	203335029	A	G	1.14 (0.94-1.37)	.183	1.12	.416	1.15	.285	.938	.004
<i>KCNS3</i>	rs1031772	2	18036181	G	A	1.10 (0.90-1.35)	.355	1.18	.277	1.04	.784	.597	<.001
<i>KCNS3</i>	rs1031771	2	18036560	T	C	1.07 (0.88-1.30)	.488	1.11	.504	1.05	.740	.858	<.001
<i>INPP4A</i>	rs3769712	2	98611961	T	A	1.03 (0.85-1.25)	.768	1.08	.614	0.99	.946	.753	.799
<i>INPP4A</i>	rs2278206	2	98630762	G	A	1.01 (0.83-1.22)	.961	1.08	.613	0.95	.694	.588	.316
<i>IL1RL1</i>	rs1420089	2	102396907	C	T	0.85 (0.60-1.21)	.373	0.58	.063	1.08	.732	.137	.005
<i>IL1RL1</i>	rs13431828	2	102413171	T	C	0.79 (0.61-1.03)	.081	0.89	.583	0.74	.075	.603	.001
<i>IL1RL1</i>	rs1041973	2	102413986	A	C	0.95 (0.77-1.17)	.630	0.99	.931	0.93	.585	.871	<.001
<i>IL1RL1</i>	rs1420101	2	102416234	T	C	1.31 (1.07-1.61)	.009	1.14	.395	1.47	.006	.268	.030
<i>IL1RL1</i>	rs1946131	2	102420447	T	C	1.35 (0.99-1.85)	.058	1.25	.414	1.41	.080	.852	<.001
<i>IL1RL1</i>	rs1921622	2	102424585	A	G	1.28 (1.06-1.56)	.011	1.24	.158	1.32	.033	.811	<.001
<i>IL1RL1</i>	rs1861245	2	102425424	T	C	0.86 (0.71-1.04)	.127	0.86	.340	0.86	.234	.930	<.001
<i>IL18R1</i>	rs1362348	2	102443142	G	C	0.88 (0.73-1.07)	.201	0.87	.377	0.89	.351	.978	<.001
<i>IL18R1</i>	rs3771166	2	102444740	A	G	0.88 (0.73-1.07)	.216	0.85	.330	0.90	.332	.861	<.001
<i>IL18R1</i>	rs1974675	2	102444893	A	G	0.88 (0.72-1.07)	.198	0.84	.290	0.90	.417	.807	<.001
<i>IL18R1</i>	rs2270297	2	102451193	T	C	0.91 (0.76-1.11)	.358	0.99	.943	0.86	.237	.516	<.001
<i>IL18R1</i>	rs3213733	2	102456402	A	C	0.89 (0.71-1.13)	.341	1.10	.619	0.79	.119	.226	<.001
<i>IL18R1</i>	rs1035130	2	102459920	T	C	1.18 (0.93-1.49)	.169	1.16	.361	1.20	.300	.996	.114
<i>IL18R1</i>	rs4851004	2	102468055	T	C	0.98 (0.82-1.18)	.851	0.90	.501	1.04	.763	.537	<.001
<i>IL18R1</i>	rs2287033	2	102469755	C	T	0.97 (0.81-1.17)	.741	0.90	.501	1.02	.903	.616	<.001
<i>IL1A</i>	rs17561	2	113253454	A	C	1.14 (0.92-1.40)	.222	1.13	.467	1.15	.325	.993	.007
<i>IL1B</i>	rs1143627	2	113310618	A	G	1.03 (0.86-1.23)	.782	1.01	.946	1.04	.750	.938	<.001
<i>IL1B</i>	rs16944	2	113311098	G	A	1.02 (0.85-1.22)	.854	0.99	.947	1.04	.750	.861	<.001
<i>IL1RN</i>	rs419598	2	113603438	C	T	0.86 (0.70-1.04)	.123	0.85	.242	0.86	.312	.982	.003
<i>IL1RN</i>	rs446433	2	113603504	A	G	0.85 (0.70-1.04)	.111	0.85	.242	0.85	.278	.936	.003
<i>IL1RN</i>	rs442710	2	113603630	A	G	0.86 (0.70-1.04)	.123	0.85	.242	0.86	.312	.982	.003
<i>IL1RN</i>	rs447713	2	113603903	G	A	0.86 (0.70-1.04)	.123	0.85	.242	0.86	.312	.982	.003
<i>IL1RN</i>	rs454078	2	113605024	T	A	0.87 (0.71-1.05)	.148	0.86	.270	0.87	.347	.985	.002
<i>IL1RN</i>	rs440286	2	113605700	A	C	0.89 (0.73-1.08)	.245	0.92	.530	0.86	.305	.835	.017
<i>IL1RN</i>	rs3087271	2	113611431	C	A	0.87 (0.72-1.06)	.156	0.96	.736	0.78	.088	.364	.001
<i>IL1RN</i>	rs895496	2	113615256	T	C	1.27 (1.04-1.55)	.017	1.35	.045	1.21	.160	.651	<.001

(Continued)

TABLE E2. (Continued)

Gene	SNP rsID	Chromosome	Position	A1	A2	Overall OR (95% CI)	P (overall)	OR (Mex)	P (Mex)	OR (PR)	P (PR)	P (het)	P (freq)
<i>DPP10</i>	rs1430090	2	114926872	C	A	0.96 (0.77-1.20)	.737	0.94	.684	0.99	.938	.897	.848
<i>DPP10</i>	rs17763180	2	114930739	T	C	0.94 (0.77-1.16)	.565	1.02	.883	0.87	.334	.493	.009
<i>DPP10</i>	rs17712682	2	114935758	A	G	0.95 (0.77-1.16)	.601	1.03	.825	0.87	.334	.461	.054
<i>DPP10</i>	rs13011555	2	114944770	C	T	0.85 (0.71-1.04)	.108	0.90	.445	0.81	.133	.679	.346
<i>DPP10</i>	rs17764091	2	114945352	G	T	0.99 (0.76-1.29)	.947	1.11	.608	0.91	.602	.552	.238
<i>DPP10</i>	rs7559909	2	114969518	A	G	0.87 (0.72-1.06)	.157	0.92	.530	0.83	.172	.682	.358
<i>DPP10</i>	rs12151526	2	114973525	T	G	0.85 (0.70-1.04)	.106	0.91	.484	0.81	.115	.613	.355
<i>DPP10</i>	rs1820924	2	114986437	T	C	1.11 (0.92-1.34)	.292	1.13	.366	1.08	.552	.881	.005
<i>DPP10</i>	rs1435879	2	115209117	G	A	1.09 (0.87-1.37)	.452	1.27	.125	0.90	.538	.175	<.001
<i>DPP10</i>	rs843385	2	115893809	C	T	1.21 (0.88-1.65)	.234	0.93	.782	1.38	.100	.316	<.001
<i>HNMT</i>	rs6755148	2	138551360	G	C	1.05 (0.87-1.27)	.596	1.32	.054	0.87	.296	.043	.003
<i>HNMT</i>	rs1349992	2	138578876	A	G	1.08 (0.89-1.30)	.444	1.02	.887	1.13	.364	.681	<.001
<i>STAT4</i>	rs3024866	2	191748347	G	A	0.96 (0.80-1.15)	.647	1.00	1.000	0.92	.520	.720	.164
<i>CTLA4</i>	rs16840252	2	204557025	T	C	1.17 (0.90-1.52)	.233	1.37	.140	1.06	.734	.423	.029
<i>CTLA4</i>	rs5742909	2	204557853	T	C	1.18 (0.81-1.72)	.389	1.42	.238	1.03	.900	.533	.530
<i>IL5RA</i>	rs2290608	3	3126759	T	C	1.08 (0.86-1.36)	.518	1.12	.567	1.06	.709	.921	<.001
<i>PPARG</i>	rs1801282	3	12368125	G	C	0.74 (0.55-1.00)	.047	0.83	.331	0.61	.049	.426	<.001
<i>PPARG</i>	rs3856806	3	12450557	T	C	0.82 (0.62-1.08)	.157	0.90	.584	0.70	.118	.468	<.001
<i>CX3CR1</i>	rs1050592	3	39281788	G	A	0.89 (0.72-1.11)	.298	1.04	.815	0.77	.090	.210	.103
<i>CX3CR1</i>	rs3732378	3	39282166	A	G	0.89 (0.66-1.20)	.443	0.90	.655	0.88	.527	.964	.608
<i>CX3CR1</i>	rs3732379	3	39282260	T	C	0.89 (0.72-1.11)	.298	1.04	.815	0.77	.090	.210	.103
<i>CCR3</i>	rs4987053	3	46281704	C	T	0.96 (0.68-1.34)	.796	1.00	1.000	0.93	.739	.972	.011
<i>TLR9</i>	rs187084	3	52236071	G	A	1.22 (1.01-1.48)	.037	1.09	.534	1.37	.021	.282	<.001
<i>CD86</i>	rs2715267	3	123253548	G	T	0.97 (0.80-1.18)	.767	1.01	.936	0.95	.660	.815	<.001
<i>CD86</i>	rs9282641	3	123279458	A	G	0.75 (0.53-1.08)	.122	0.71	.274	0.78	.264	.963	.001
<i>CD86</i>	rs9831894	3	123283177	C	A	1.04 (0.86-1.26)	.699	1.02	.890	1.06	.686	.932	<.001
<i>CD86</i>	rs2332096	3	123303833	T	G	1.01 (0.84-1.23)	.883	1.05	.762	0.99	.949	.862	<.001
<i>CD86</i>	rs2681417	3	123307887	G	A	0.97 (0.71-1.34)	.871	1.20	.547	0.89	.564	.522	<.001
<i>MYLK</i>	rs4678047	3	124935528	G	A	0.99 (0.82-1.19)	.925	1.09	.526	0.91	.484	.398	<.001
<i>TLR10</i>	rs11096957	4	38599057	G	T	1.14 (0.95-1.37)	.151	1.18	.248	1.12	.364	.835	<.001
<i>TLR6</i>	rs5743810	4	38652916	A	G	1.19 (0.93-1.51)	.161	1.14	.503	1.22	.206	.869	.008
<i>IL8</i>	rs2227306	4	74972090	T	C	1.03 (0.84-1.26)	.797	1.02	.877	1.03	.836	.935	.860
<i>IL8</i>	rs2227543	4	74972945	T	C	1.04 (0.85-1.27)	.720	1.02	.877	1.05	.732	.993	.785
<i>PGDS</i>	rs2171381	4	95581946	T	A	0.98 (0.82-1.17)	.816	0.82	.146	1.13	.315	.097	<.001
<i>PGDS</i>	rs2289186	4	95612815	T	G	1.04 (0.86-1.25)	.704	1.28	.074	0.85	.235	.044	<.001
<i>IL2</i>	rs2069762	4	123735585	C	A	0.80 (0.66-0.97)	.025	0.80	.108	0.81	.120	.981	.611
<i>IL15</i>	rs10519613	4	143011689	A	C	0.97 (0.79-1.20)	.793	1.11	.423	0.78	.149	.128	<.001
<i>PDE4D</i>	rs1588265	5	59405551	G	A	0.96 (0.78-1.17)	.682	0.89	.440	1.02	.891	.572	.032
<i>PDE4D</i>	rs1544791	5	59474839	T	C	0.99 (0.82-1.20)	.921	0.89	.448	1.07	.603	.415	<.001
<i>PDE4D</i>	rs983280	5	59480894	C	T	1.00 (0.82-1.21)	1.000	0.87	.360	1.11	.435	.270	<.001
<i>CSF2</i>	rs2069616	5	131435976	G	A	1.02 (0.84-1.23)	.882	1.09	.588	0.97	.798	.631	<.001
<i>CSF2</i>	rs25881	5	131439037	T	C	1.12 (0.90-1.38)	.305	1.01	.939	1.23	.170	.419	.084
<i>CSF2</i>	rs25882	5	131439359	C	T	1.12 (0.91-1.38)	.292	0.99	.940	1.26	.123	.305	.270
<i>IL5</i>	rs743562	5	131900282	T	C	0.96 (0.80-1.17)	.696	1.03	.827	0.91	.469	.583	.002
<i>IL5</i>	rs2069812	5	131907815	A	G	1.01 (0.84-1.22)	.924	0.95	.716	1.06	.656	.638	<.001
<i>RAD50</i>	rs2244012	5	131929124	G	A	1.41 (1.13-1.75)	.002	1.31	.120	1.48	.006	.679	.003
<i>IL13</i>	rs20541	5	132023863	A	G	1.11 (0.90-1.36)	.320	1.09	.536	1.14	.420	.917	<.001
<i>IL4</i>	rs2070874	5	132037609	T	C	1.08 (0.89-1.32)	.425	0.99	.945	1.20	.216	.397	<.001
<i>IL4</i>	rs2227284	5	132040624	G	T	0.98 (0.81-1.18)	.807	1.17	.285	0.83	.178	.108	<.001
<i>CD14</i>	rs2569190	5	139993100	A	G	0.94 (0.79-1.13)	.517	0.94	.647	0.94	.647	.926	.001
<i>CD14</i>	rs2569193	5	139995679	A	G	1.11 (0.90-1.37)	.313	1.09	.590	1.14	.379	.911	.954
<i>SCGB3A2</i>	rs1368408	5	147238355	A	G	0.92 (0.76-1.12)	.419	0.82	.143	1.08	.641	.228	<.001
<i>SPINK5</i>	rs2303063	5	147460220	G	A	1.01 (0.84-1.21)	.925	1.20	.185	0.87	.276	.105	<.001
<i>SPINK5</i>	rs2303067	5	147461148	A	G	1.00 (0.83-1.20)	.962	1.19	.208	0.85	.221	.097	<.001
<i>ADRB2</i>	rs12654778	5	148185934	A	G	0.94 (0.78-1.12)	.490	0.88	.302	1.01	.948	.498	.048
<i>ADRB2</i>	rs1042713	5	148186633	A	G	0.92 (0.77-1.10)	.360	0.89	.364	0.95	.699	.781	.773
<i>ADRB2</i>	rs1042714	5	148186666	G	C	0.98 (0.80-1.21)	.875	1.23	.233	0.86	.255	.125	<.001
<i>HAVCR1</i>	rs2277025	5	156392673	C	T	1.04 (0.86-1.26)	.693	1.03	.836	1.05	.723	.991	<.001
<i>HAVCR2</i>	rs10515746	5	156469146	A	C	1.22 (0.96-1.56)	.107	1.50	.074	1.12	.456	.344	<.001
<i>CYFIP2</i>	rs2288068	5	156646715	A	G	1.11 (0.82-1.50)	.494	1.10	.663	1.12	.596	.924	.619
<i>CYFIP2</i>	rs6555977	5	156740934	C	T	0.82 (0.61-1.10)	.177	0.79	.187	0.88	.668	.872	<.001
<i>CYFIP2</i>	rs17599222	5	156749844	G	T	0.88 (0.74-1.06)	.171	0.81	.124	0.95	.662	.460	<.001

(Continued)

TABLE E2. (Continued)

Gene	SNP rsID	Chromosome	Position	A1	A2	Overall OR (95% CI)	P (overall)	OR (Mex)	P (Mex)	OR (PR)	P (PR)	P (het)	P (freq)
<i>CYFIP2</i>	rs3734034	5	156753795	T	C	1.03 (0.86-1.24)	.740	0.89	.405	1.17	.217	.175	.523
<i>IL12B</i>	rs3212227	5	158675528	G	T	1.01 (0.83-1.21)	.962	0.96	.782	1.05	.740	.738	.012
<i>IL12B</i>	rs2546890	5	158692478	A	G	0.90 (0.75-1.09)	.293	1.01	.944	0.82	.134	.328	<.001
<i>ADRA1B</i>	rs10515807	5	159297576	A	G	1.15 (0.91-1.44)	.243	0.84	.304	1.51	.011	.018	.628
<i>LTC4S</i>	rs730012	5	179153244	C	A	1.03 (0.82-1.29)	.818	0.88	.439	1.17	.314	.257	.053
<i>EDN1</i>	rs1476046	6	12401207	A	G	0.90 (0.72-1.12)	.341	0.79	.155	1.00	1.000	.345	.084
<i>EDN1</i>	rs5370	6	12404241	T	G	0.82 (0.65-1.03)	.083	0.77	.128	0.86	.343	.727	.545
<i>HLA-G</i>	rs1736936	6	29902296	G	A	1.08 (0.91-1.29)	.391	1.06	.645	1.10	.457	.932	.465
<i>LTA</i>	rs909253	6	31648292	G	A	1.03 (0.86-1.24)	.747	0.96	.737	1.10	.446	.500	.482
<i>TNF</i>	rs1799964	6	31650287	C	T	1.07 (0.85-1.34)	.562	1.34	.106	0.91	.544	.131	.017
<i>LTA</i>	rs1800630	6	31650455	A	C	1.07 (0.83-1.40)	.593	1.41	.112	0.90	.547	.139	.012
<i>LTA</i>	rs1800629	6	31651010	A	G	1.03 (0.75-1.40)	.875	0.83	.500	1.14	.499	.438	<.001
<i>PLA2G7</i>	rs1051931	6	46780902	A	G	0.92 (0.73-1.15)	.448	0.87	.458	0.95	.707	.825	<.001
<i>PLA2G7</i>	rs16874954	6	46785057	A	C	0.33 (0.03-3.21)	.317	0.00	.157	1.00	1.000	1.000	.711
<i>PLA2G7</i>	rs1805018	6	46787262	G	A	0.98 (0.68-1.42)	.926	1.82	.106	0.79	.275	.082	<.001
<i>NA</i>	rs8193036	6	52158452	C	T	0.99 (0.72-1.35)	.937	1.11	.655	0.88	.574	.578	.286
<i>NA</i>	rs2275913	6	52158992	A	G	0.90 (0.73-1.12)	.356	0.87	.408	0.93	.614	.854	.016
<i>IL17F</i>	rs763780	6	52209698	C	T	0.86 (0.55-1.34)	.502	0.95	.876	0.77	.423	.809	.342
<i>ARG1</i>	rs2781659	6	131933513	G	A	0.98 (0.82-1.18)	.851	1.12	.388	0.86	.257	.188	<.001
<i>IFNGR1</i>	rs1887415	6	137560931	G	A	1.38 (0.90-2.11)	.136	1.30	.310	1.60	.239	.838	<.001
<i>IL6</i>	rs1800795	7	22539885	C	G	1.01 (0.80-1.27)	.952	1.02	.917	1.00	1.000	.967	<.001
<i>NOD1</i>	rs2907749	7	30258981	G	A	0.97 (0.81-1.17)	.773	1.30	.056	0.73	.021	.004	.033
<i>NPSR1</i>	rs184448	7	34546350	A	C	1.08 (0.90-1.30)	.381	1.16	.257	1.02	.899	.523	<.001
<i>NPSR1</i>	rs324396	7	34563363	T	C	0.88 (0.72-1.08)	.223	0.81	.117	0.99	.939	.373	<.001
<i>NPSR1</i>	rs324957	7	34574612	G	A	1.06 (0.89-1.27)	.520	1.14	.320	0.99	.949	.502	<.001
<i>NPSR1</i>	rs324960	7	34575631	T	C	1.15 (0.94-1.40)	.172	1.56	.007	0.95	.699	.025	<.001
<i>NPSR1</i>	rs740347	7	34585542	C	G	1.46 (1.07-2.00)	.018	3.08	<.001	1.06	.772	.006	<.001
<i>NPSR1</i>	rs324981	7	34591353	T	A	0.95 (0.78-1.14)	.566	0.94	.674	0.95	.694	.953	<.001
<i>NPSR1</i>	rs325462	7	34623086	T	A	0.97 (0.81-1.17)	.743	0.96	.786	0.98	.847	.977	<.001
<i>CCL26</i>	rs2302009	7	75043649	C	A	0.97 (0.80-1.17)	.731	0.96	.812	0.97	.803	.945	<.001
<i>CCL24</i>	rs4732416	7	75086413	C	T	0.96 (0.80-1.16)	.672	0.83	.168	1.10	.480	.162	.389
<i>CCL24</i>	rs2302005	7	75087410	A	G	0.93 (0.76-1.13)	.456	0.89	.375	0.98	.885	.688	<.001
<i>CCL24</i>	rs2302004	7	75087506	A	G	1.09 (0.91-1.30)	.363	1.16	.283	1.03	.805	.595	<.001
<i>NOS3</i>	rs2070744	7	150127727	—	T	1.00 (0.06-15.99)	1.000	0.00	.317	NA	.317	1.000	.537
<i>NOS3</i>	rs1799983	7	150133759	T	G	0.97 (0.77-1.23)	.814	1.17	.327	0.79	.176	.125	.554
<i>DEFB1</i>	rs11362	8	6722809	T	C	1.11 (0.93-1.32)	.259	1.16	.283	1.07	.583	.737	<.001
<i>DEFB1</i>	rs2741136	8	6724606	G	A	0.98 (0.81-1.19)	.848	0.87	.332	1.09	.506	.287	.003
<i>NAT2</i>	rs1801280	8	18302134	C	T	1.04 (0.86-1.24)	.709	1.12	.456	0.99	.905	.575	<.001
<i>NAT2</i>	rs1799929	8	18302274	T	C	1.05 (0.87-1.26)	.605	1.11	.504	1.02	.903	.730	<.001
<i>NAT2</i>	rs1799930	8	18302383	A	G	1.10 (0.88-1.38)	.421	1.09	.652	1.11	.501	.972	.003
<i>NAT2</i>	rs1208	8	18302596	G	A	1.03 (0.86-1.23)	.749	1.10	.521	0.99	.905	.634	<.001
<i>CHRNA2</i>	rs11778371	8	27375822	T	C	1.00 (0.59-1.71)	1.000	0.63	.405	1.16	.639	.524	.001
<i>IL33</i>	rs1342326	9	6180076	C	A	1.65 (1.29-2.11)	<.001	1.58	.029	1.68	.001	.922	<.001
<i>TLE4</i>	rs2378383	9	79268916	G	A	0.95 (0.74-1.23)	.699	1.13	.480	0.78	.186	.187	.005
<i>IKBKAP</i>	rs1538660	9	108721380	A	G	1.02 (0.80-1.30)	.853	1.27	.235	0.89	.475	.212	.005
<i>IKBKAP</i>	rs3204145	9	108731175	T	A	1.05 (0.82-1.33)	.711	1.29	.200	0.92	.579	.223	.009
<i>TLR4</i>	rs4986790	9	117554856	G	A	0.96 (0.56-1.67)	.889	1.25	.637	0.83	.602	.692	.264
<i>C5</i>	rs17611	9	120848754	T	C	1.19 (1.00-1.41)	.050	1.10	.459	1.28	.043	.418	<.001
<i>C5</i>	rs25681	9	120859559	A	G	0.96 (0.82-1.11)	.563	0.92	.430	1.00	1.000	.645	<.001
<i>NA</i>	rs4143094	10	8129142	T	G	1.19 (0.96-1.48)	.111	1.40	.076	1.10	.496	.358	<.001
<i>GATA3</i>	rs1058240	10	8156604	G	A	0.85 (0.64-1.12)	.251	0.82	.399	0.87	.421	.963	.006
<i>GATA3</i>	rs379568	10	8165825	A	G	0.93 (0.73-1.19)	.579	0.81	.230	1.08	.657	.303	.011
<i>ALOX5</i>	rs892691	10	45237098	A	G	1.01 (0.83-1.22)	.961	0.93	.639	1.06	.661	.589	<.001
<i>BDNF</i>	rs6265	11	27636492	T	C	1.03 (0.81-1.32)	.801	1.08	.692	1.00	1.000	.859	.005
<i>BDNF</i>	rs11030101	11	27637320	T	A	1.03 (0.85-1.25)	.732	1.06	.670	1.01	.946	.869	.020
<i>BDNF</i>	rs2049045	11	27650817	C	G	1.17 (0.88-1.57)	.273	1.32	.294	1.12	.538	.710	<.001
<i>MS4A2</i>	rs569108	11	59619680	G	A	1.44 (0.86-2.40)	.159	1.71	.251	1.33	.355	.872	.004
<i>MS4A2</i>	rs2847655	11	59622247	C	T	0.90 (0.73-1.10)	.300	0.62	.004	1.16	.281	.005	<.001
<i>SCGB1A1</i>	rs3741240	11	61943118	A	G	1.21 (1.00-1.47)	.055	1.26	.093	1.16	.312	.756	<.001
<i>IL18</i>	rs549908	11	111526126	G	T	1.04 (0.86-1.26)	.695	1.17	.278	0.94	.641	.310	.596
<i>IL18</i>	rs5744247	11	111531366	C	G	0.89 (0.67-1.19)	.419	0.98	.924	0.77	.251	.502	<.001
<i>AICDA</i>	rs2028373	12	8648748	G	A	0.98 (0.82-1.18)	.816	0.92	.534	1.03	.801	.592	<.001

(Continued)

TABLE E2. (Continued)

Gene	SNP rsID	Chromosome	Position	A1	A2	Overall OR (95% CI)	P (overall)	OR (Mex)	P (Mex)	OR (PR)	P (PR)	P (het)	P (freq)
VDR	rs11608702	12	46515035	T	A	0.92 (0.76-1.10)	.347	0.90	.398	0.94	.633	.887	<.001
VDR	rs7975232	12	46525104	A	C	1.01 (0.84-1.21)	.927	1.09	.504	0.94	.614	.459	<.001
VDR	rs1544410	12	46526102	T	C	0.88 (0.73-1.07)	.201	0.79	.127	0.95	.700	.413	<.001
VDR	rs2239182	12	46541678	C	T	0.96 (0.80-1.15)	.652	0.98	.896	0.94	.620	.877	<.001
VDR	rs1540339	12	46543593	T	C	1.00 (0.82-1.21)	.961	0.95	.727	1.04	.786	.732	.149
VDR	rs2239179	12	46544033	C	T	0.96 (0.80-1.15)	.678	0.95	.686	0.98	.849	.943	.730
VDR	rs3782905	12	46552434	C	G	0.93 (0.77-1.12)	.449	0.94	.628	0.93	.559	.962	.544
VDR	rs2239186	12	46555677	G	A	1.07 (0.84-1.35)	.586	0.95	.752	1.26	.221	.309	<.001
VDR	rs2853564	12	46564754	A	G	0.92 (0.75-1.13)	.436	0.83	.237	1.00	1.000	.432	.003
STAT6	rs324015	12	55776367	T	C	1.03 (0.84-1.26)	.795	1.27	.096	0.82	.177	.043	<.001
STAT6	rs324011	12	55788449	T	C	1.12 (0.93-1.33)	.234	1.04	.784	1.18	.177	.547	<.001
STAT6	rs167769	12	55790042	T	C	1.13 (0.94-1.35)	.199	1.08	.583	1.16	.218	.748	<.001
IRAK3	rs1882200	12	64883968	T	C	0.94 (0.76-1.15)	.532	0.84	.265	1.02	.890	.408	<.001
IRAK3	rs1821777	12	64892495	T	C	0.93 (0.75-1.14)	.464	0.85	.303	0.99	.945	.532	<.001
IRAK3	rs1624395	12	64904483	A	G	0.98 (0.81-1.18)	.807	0.91	.504	1.03	.795	.565	<.001
IFNG	rs2069727	12	66834490	C	T	0.98 (0.81-1.20)	.878	0.92	.590	1.04	.785	.630	.007
LTA4H	rs1978331	12	94911669	G	A	0.93 (0.77-1.12)	.443	0.79	.119	1.04	.753	.194	<.001
ALOX5AP	rs10507391	13	30210096	T	A	0.85 (0.71-1.01)	.071	0.82	.129	0.88	.293	.764	.132
ALOX5AP	rs9315050	13	30234045	G	A	1.11 (0.77-1.58)	.584	0.97	.895	1.25	.378	.602	.972
RNASE3	rs2073342	14	20430056	C	G	1.08 (0.87-1.35)	.472	1.23	.288	1.02	.893	.498	<.001
PTGDR	rs708487	14	51810831	G	A	0.97 (0.75-1.26)	.845	1.31	.227	0.83	.256	.131	<.001
ARG2	rs3759757	14	67147580	C	G	1.12 (0.93-1.34)	.240	1.28	.068	0.98	.896	.190	.004
ARG2	rs17249437	14	67170640	C	T	1.04 (0.87-1.24)	.680	1.05	.694	1.03	.848	.955	.578
ARG2	rs3742879	14	67184754	G	A	1.12 (0.87-1.45)	.368	1.04	.843	1.19	.311	.705	.013
SERPINA3	rs4934	14	94150556	A	G	1.02 (0.85-1.23)	.812	0.79	.101	1.26	.073	.020	<.001
SMAD3	rs744910	15	65233839	A	G	1.07 (0.89-1.28)	.488	1.16	.279	0.99	.950	.458	.998
IL16	rs4778889	15	79376050	C	T	1.05 (0.85-1.29)	.672	1.15	.408	0.98	.891	.537	<.001
IL4R	rs1805011	16	27281373	C	A	0.85 (0.68-1.07)	.164	0.87	.458	0.84	.236	.967	.004
IL4R	rs2234898	16	27281416	T	G	0.88 (0.70-1.10)	.248	0.87	.458	0.88	.376	.931	.002
IL4R	rs1805015	16	27281681	C	T	0.88 (0.70-1.10)	.256	0.90	.578	0.87	.315	.955	<.001
NOD2	rs5743291	16	49314777	A	G	1.08 (0.76-1.53)	.657	1.19	.515	1.00	1.000	.765	.539
NOD2	rs1077861	16	49317048	T	A	0.92 (0.76-1.10)	.334	0.90	.451	0.93	.535	.960	<.001
NOD2	rs3135499	16	49323628	C	A	1.01 (0.84-1.22)	.888	0.99	.945	1.03	.799	.897	.002
NQO1	rs1800566	16	68302646	A	G	1.19 (0.98-1.44)	.078	1.07	.623	1.31	.048	.352	<.001
NQO1	rs2917666	16	68321461	C	G	1.10 (0.92-1.32)	.287	1.06	.679	1.14	.289	.756	.251
CYBA	rs4673	16	87240737	A	G	1.04 (0.83-1.29)	.739	0.86	.405	1.16	.297	.240	<.001
NOS2	rs2297518	17	23120724	A	G	1.00 (0.79-1.27)	1.000	0.90	.612	1.06	.709	.614	<.001
NOS2	rs1137933	17	23130059	A	G	0.96 (0.77-1.20)	.734	0.96	.847	0.96	.779	.913	<.001
CCL11	rs4795895	17	29635559	A	G	0.83 (0.64-1.10)	.191	0.87	.513	0.81	.249	.937	.072
CCL11	rs17809012	17	29636557	G	A	0.99 (0.82-1.20)	.923	1.02	.880	0.97	.800	.857	<.001
CCL11	rs3744508	17	29637007	A	G	0.94 (0.73-1.20)	.612	0.75	.143	1.10	.558	.172	.500
CCL5	rs2280788	17	31231518	C	G	1.90 (0.88-4.09)	.095	1.40	.564	2.40	.090	.774	.629
IKZF3	rs9303277	17	35229995	T	C	0.80 (0.66-0.96)	.017	0.70	.012	0.88	.323	.244	<.001
ZBP2	rs12936231	17	35282646	G	C	0.80 (0.67-0.96)	.019	0.73	.026	0.86	.238	.416	<.001
GSDMB	rs8067378	17	35304874	G	A	0.81 (0.67-0.98)	.027	0.73	.030	0.88	.289	.393	<.001
GSDMB	rs2305480	17	35315722	A	G	0.67 (0.55-0.82)	<.001	0.71	.023	0.64	.001	.721	<.001
GSDMB	rs2305479	17	35315743	T	C	0.70 (0.58-0.85)	<.001	0.74	.046	0.67	.003	.674	.002
GSDMB	rs2290400	17	35319766	C	T	0.76 (0.63-0.91)	.003	0.71	.020	0.79	.062	.650	<.001
GSDMB	rs7216389	17	35323475	C	T	0.70 (0.57-0.85)	<.001	0.72	.028	0.68	.004	.834	<.001
GSDMB	rs9303281	17	35327572	G	A	0.77 (0.64-0.93)	.006	0.69	.011	0.83	.148	.382	<.001
GSDMB	rs7219923	17	35328044	C	T	0.76 (0.63-0.92)	.004	0.71	.020	0.80	.069	.632	<.001
ORMDL3	rs8076131	17	35334438	G	A	0.68 (0.56-0.83)	<.001	0.69	.015	0.67	.004	.983	<.001
ORMDL3	rs12603332	17	35336333	T	C	0.79 (0.65-0.95)	.012	0.66	.005	0.90	.383	.137	<.001
ORMDL3	rs3744246	17	35337876	T	C	0.90 (0.73-1.11)	.333	0.72	.054	1.05	.726	.111	<.001
ORMDL3	rs4795405	17	35341943	T	C	0.71 (0.59-0.86)	<.001	0.65	.003	0.76	.039	.453	<.001
ORMDL3	rs8079416	17	35346239	T	C	0.81 (0.67-0.97)	.025	0.69	.008	0.93	.532	.138	<.001
ORMDL3	rs4795408	17	35361153	A	G	1.21 (1.01-1.45)	.042	1.55	.001	0.98	.850	.018	<.001
ORMDL3	rs3894194	17	35375519	A	G	1.22 (1.01-1.46)	.034	1.55	.001	0.99	.950	.022	<.001
ORMDL3	rs3859192	17	35382174	T	C	1.05 (0.87-1.26)	.607	0.99	.945	1.10	.442	.631	.477
ORMDL3	rs11650680	17	35832762	T	C	0.91 (0.74-1.13)	.391	0.85	.291	0.98	.879	.598	.381
ITGB3	rs2317385	17	42684681	A	G	1.04 (0.81-1.33)	.753	1.06	.763	1.03	.872	.996	.001
ITGB3	rs2015729	17	42709492	A	G	1.07 (0.89-1.30)	.467	1.08	.603	1.07	.609	.970	<.001

(Continued)

TABLE E2. (Continued)

Gene	SNP rsID	Chromosome	Position	A1	A2	Overall OR (95% CI)	P (overall)	OR (Mex)	P (Mex)	OR (PR)	P (PR)	P (het)	P (freq)
<i>ITGB3</i>	rs1000232	17	42711560	C	T	1.09 (0.90-1.32)	.383	1.12	.459	1.07	.609	.898	<.001
<i>ITGB3</i>	rs2292867	17	42712488	T	C	1.13 (0.88-1.44)	.348	0.96	.833	1.23	.186	.409	<.001
<i>ITGB3</i>	rs999323	17	42726602	C	T	1.06 (0.86-1.31)	.559	1.13	.438	1.01	.942	.682	.126
<i>ITGB3</i>	rs3760372	17	42735001	T	C	1.05 (0.87-1.27)	.595	1.04	.789	1.07	.623	.940	<.001
<i>ITGB3</i>	rs3809863	17	42740011	T	C	1.00 (0.83-1.20)	1.000	0.95	.726	1.04	.749	.704	<.001
<i>ITGB3</i>	rs2317676	17	42743282	G	A	0.94 (0.70-1.27)	.704	0.89	.674	0.97	.856	.930	<.001
<i>TBX21</i>	rs4794067	17	43163827	C	T	1.09 (0.90-1.32)	.375	1.01	.946	1.19	.221	.455	<.001
<i>TBX21</i>	rs11650354	17	43177091	T	C	1.18 (0.91-1.54)	.205	1.23	.307	1.15	.428	.904	.025
<i>TBX21</i>	rs16947078	17	43180499	G	A	1.17 (0.93-1.47)	.182	1.15	.462	1.18	.262	.987	<.001
<i>TBXA2R</i>	rs8113232	19	3537543	A	G	1.19 (0.71-2.01)	.508	2.00	.248	1.05	.882	.525	<.001
<i>TBXA2R</i>	rs4523	19	3546794	G	A	1.05 (0.87-1.26)	.636	1.06	.713	1.04	.757	.989	<.001
<i>TBXA2R</i>	rs3786989	19	3555004	C	G	1.57 (0.61-4.05)	.346	3.00	.317	1.33	.593	.948	.063
<i>TGFB1</i>	rs1800469	19	46552136	A	G	1.11 (0.92-1.33)	.285	1.02	.894	1.19	.174	.449	<.001
<i>ADAM33</i>	rs2280089	20	3598127	A	G	0.83 (0.62-1.12)	.228	0.69	.096	0.98	.918	.314	.731
<i>ADAM33</i>	rs2280091	20	3598234	G	A	0.83 (0.62-1.12)	.228	0.69	.096	0.98	.918	.314	.731
<i>ADAM33</i>	rs3918395	20	3601149	A	C	0.83 (0.62-1.12)	.228	0.69	.096	0.98	.918	.314	.731
<i>PRNP</i>	rs6052761	20	4605017	C	T	1.06 (0.81-1.38)	.683	1.24	.297	0.94	.719	.375	.231
<i>ADA</i>	rs244076	20	42686329	C	T	1.13 (0.91-1.41)	.265	1.09	.612	1.17	.299	.849	.079
<i>MMP9</i>	rs3918241	20	44069142	A	T	1.15 (0.85-1.55)	.360	0.88	.617	1.35	.124	.238	.001
<i>MMP9</i>	rs2274755	20	44073099	T	G	1.21 (0.89-1.64)	.217	0.88	.617	1.48	.050	.147	.002
<i>MMP9</i>	rs17576	20	44073632	G	A	1.16 (0.94-1.42)	.161	0.96	.814	1.34	.038	.146	.010
<i>IL2RB</i>	rs2284033	22	35858534	A	G	1.07 (0.89-1.28)	.465	1.01	.948	1.13	.338	.594	.496

A1, major allele; A2, minor allele; Mex, Mexicans; Position, chromosomal position; P (freq), P value for heterogeneity in minor allele frequency; P (het), P value for heterogeneity of effect; PR, Puerto Ricans.

TABLE E3. Gene-based replication of prior genetic associations in both Mexicans and Puerto Ricans

Gene	SNP rsID	Chromosome	Overall OR	95% CI	<i>P</i> (overall)	<i>P</i> (adjusted)	OR (MX)	OR (PR)	<i>P</i> (het)	<i>P</i> (freq)
A. Genes associated in overall population with no significant heterogeneity										
<i>RAD50</i>	rs2706347	5	1.39	1.12-1.74	.003	.02	1.23	1.48	.50	.0007
<i>HLA-DQB1</i>	rs34485459	6	0.75	0.60-0.94	.01	.03	0.68	0.82	.49	.001
<i>IL16</i>	rs3726	15	1.34	1.11-1.61	.002	.03	1.48	1.27	.49	<.0001
<i>ZPBP2</i>	rs12936231	17	0.80	0.66-0.96	.02	.03	0.72	0.85	.43	<.0001
<i>GSDMB</i>	rs4795400	17	0.67	0.55-0.82	.0001	.0002	0.72	0.62	.55	.0007
<i>ORMDL3</i>	rs17608925	17	0.57	0.41-0.80	.0009	.002	0.50	0.60	.75	.65
B. Genes associated in one population with significant heterogeneity										
<i>HNMT</i>	rs3100725	2	0.83	0.69-1.01	.07	.21	0.99	0.66*	.06	<.0001
<i>ADRA1B</i>	rs6884129	5	1.22	0.86-1.71	.26	.88	2.50*	0.91	.02	<.0001
<i>NOS3</i>	rs891512	7	0.60	0.45-0.80	.0004	.001	0.92	0.48*	.05	.02
<i>NPSR1</i>	rs182718	7	1.28	1.01-1.64	.04	.60	2.00*	1.05	.02	<.0001
<i>MS4A2</i>	rs2847666	11	0.89	0.73-1.10	.27	.30	0.65*	1.14	.01	<.0001

MX, Mexicans; *P* (adjusted), Gene-wide *P* value (adjusted for multiple comparisons); *P* (freq), *P* value for heterogeneity in minor allele frequency; *P* (het), *P* value for heterogeneity of effect; *PR*, Puerto Ricans.

*Population in which there is a significant association.

TABLE E4. Assessment of heterogeneity between GALA sites

Gene	SNP rsID	τ	P_h	P_h ethnicity	τ Residual
<i>ADRA1B</i>	rs10515807	0.050	.14	.03	0.0
<i>NPSR1</i>	rs740347	0.380	.008	.02	0.081
<i>NOD1</i>	rs2907749	0.076	.03	.004	0.0
<i>MS4A2</i>	rs2847655	0.103	.02	.04	0.019
<i>ORMDL3</i>	rs4795408	0.111	.007	.19	0.077

P_h , P value for the test of heterogeneity between sites; P_h ethnicity, P value for the test of homogeneity between ethnicities in the context of heterogeneity between sites; τ , magnitude of between-site heterogeneity; τ Residual, residual amount of heterogeneity between sites once we have accounted for the heterogeneity between ethnicities.