Genome-wide association study and admixture mapping identify different asthma-associated loci in Latinos: The Genes-environments & Admixture in Latino Americans study

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Background: Asthma is a complex disease with both genetic and environmental causes. Genome-wide association studies of asthma have mostly involved European populations, and replication of positive associations has been inconsistent.

Objective: We sought to identify asthma-associated genes in a large Latino population with genome-wide association analysis and admixture mapping.

Methods: Latino children with asthma (n = 1893) and healthy control subjects (n = 1881) were recruited from 5 sites in the United States: Puerto Rico, New York, Chicago, Houston, and the San Francisco Bay Area. Subjects were genotyped on an Affymetrix World Array IV chip. We performed genome-wide association and admixture mapping to identify asthma-associated loci.

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Results: We identified a significant association between ancestry and asthma at 6p21 (lowest *P* value: rs2523924, $P < 5 \times 10^{-6}$). This association replicates in a meta-analysis of the EVE Asthma Consortium ($P = .01$). Fine mapping of the region in this study and the EVE Asthma Consortium suggests an association between *PSORS1C1* and asthma. We confirmed the strong allelic association between SNPs in the 17q21 region and asthma in Latinos (*IKZF3*, lowest *P* value: rs90792, odds ratio, 0.67; 95% CI, 0.61-0.75; $P = 6 \times 10^{-13}$) and replicated associations in several genes that had previously been associated with asthma in genome-wide association studies.

Conclusions: Admixture mapping and genome-wide association are complementary techniques that provide evidence for multiple asthma-associated loci in Latinos. Admixture mapping identifies a novel locus on 6p21 that replicates in a meta-analysis of several Latino populations, whereas genome-wide association confirms the previously identified locus on 17q21. (J Allergy Clin Immunol 2014;134:295-305.)

Key words: *Asthma, Latinos, admixture mapping, genome-wide association study, local ancestry, 17q21, 6p21*

Asthma is the most common chronic disease among children. In the United States childhood asthma prevalence is highest among Puerto Ricans (18.4%), followed by blacks (14.6%), whites (8.2%), and Mexicans (4.8%).[1,2] The discrepancy in asthma burden, as well as the paucity of studies of asthma in Latinos, has led the American Academy of Pediatrics to identify asthma among Latinos as an urgent priority for further research.[3]

Genetic variation between populations might account for some of these differences. Estimates of the heritability of asthma based on twin studies range from between 75%[4] and 92%.[5] However, few genetic loci show consistent associations across studies.[6-8] Of the 48 genes reported to be associated with asthma in genome-wide studies,[9] only 5 have been identified in more than 1 genome-wide association study (GWAS).[10-16] This might be due to differences in study designs, differences in environment between study populations, and heterogeneity in asthma phenotypes.[17,18] Our previous work has found that few genes associated with asthma replicate in Latino populations. Most that do replicate are consistent across Latino ethnic groups; however, 5 genes replicated in either Mexicans or Puerto Ricans (but not both) and showed significant heterogeneity in their association with asthma.[6] These observed differences in genetic variation might in part explain the discrepancy in asthma prevalence between the 2 groups.[19]

Most GWASs of asthma have been conducted in European and European American populations.[20] The recent identification of *PYHIN1*, a gene associated with asthma in subjects of African descent but not in Latinos or European Americans,[10] highlights the importance of studying diverse populations in genetic association analyses. Moreover, studies in non-European populations might help uncover some of the "missing heritability" in complex diseases and could provide insights into racial/ethnic disparities in asthma prevalence and severity.

Admixture mapping is a technique that can help identify asthma-associated loci in populations of mixed ancestry (eg, African Americans and Latinos).[21] In these admixed populations it is possible to use dense genotyping to estimate ancestry at a locus-specific (local) level.[22,23] If the allele frequency of risk variants is higher in one ancestral population than in others, there will be a correlation between ancestry at that locus and disease. Comparing local ancestry in subjects with disease with that seen in control subjects will show a deviation from the expected distribution of ancestry. Like GWASs, admixture mapping provides an unbiased method to screen for disease-associated loci. However, because admixture is a relatively recent phenomenon, ancestry blocks are significantly larger than haplotype blocks.[24,25] Therefore admixture mapping offers increased coverage of genetic variation and a lower multiple testing burden than GWAS, although this also means that admixture mapping peaks cover an area in the hundreds of kilobases, which makes narrowing down the causal variant more difficult. Admixture mapping has successfully identified disease-associated loci in breast[26] and prostate[27] cancer, renal disease,[28,29] and white blood cell counts,[30,31] among others. Our own prior admixture mapping study demonstrated that admixture mapping peaks preferentially harbored asthma-associated genes,[32] whereas an admixture mapping study in African Americans and Puerto Ricans identified a locus on 6q14.1 that harbored a risk allele for asthma exclusively in subjects with local European admixture.[33]

To identify genetic risk factors for asthma, we used genotype data from the Genes-environments & Admixture in Latino Americans (GALA II) study. GALA II is an ongoing, multicenter, case-control study to identify novel clinical and genetic risk factors associated with asthma and related phenotypes in Latino populations at 5 sites in the United States: Puerto Rico, New York, Chicago, Houston, and the San Francisco Bay Area, which includes genome-wide genotype data on 3774 participants. We hypothesize that by using a large population of Latino participants, we would identify novel loci for asthma.

METHODS

Recruitment and genotyping

Institutional review boards at the University of California, San Francisco, and recruitment sites approved the study, and all participants/parents provided appropriate written assent/consent. Latino children were enrolled as a part of the ongoing GALA II case-control study. From July 2006 through June 2011, when genotyping began, a total of 4045 children (1976 participants with asthma and 2065 healthy control subjects) were recruited from 5 centers (Chicago, Bronx, Houston, San Francisco Bay Area, and Puerto Rico) through a combination of community and clinic-based recruitment. Participants were eligible if they were 8 to 21 years of age, self-identified as Latino, and had 4 Latino grandparents. Asthma cases were defined as participants with a history of physician-diagnosed asthma and the presence of 2 or more symptoms of coughing, wheezing, or shortness of breath in the 2 years preceding enrollment. Participants were excluded if they reported any of the following: (1) 10 or more pack years of smoking; (2) any smoking within 1 year of recruitment date; (3) history of lung diseases other than asthma (cases) or chronic illness (cases and control subjects); or (4) pregnancy in the third trimester. Details of recruitment are described elsewhere[34] and in the Methods section in this article's Online Repository at www.jacionline.org.

Participants were genotyped at 818,154 single nucleotide polymorphisms (SNPs) on the Affymetrix Axiom World Array IV.[35] Details of individual and SNP quality control procedures are described in the Methods section in this article's Online Repository.

Ancestry was estimated by using the program ADMIXTURE, with a 3-population model.[36] Details of the ancestral populations are described in the Methods section in this article's Online Repository. Local ancestry at all positions across the genome was estimated by using the program LAMPLD,[22] assuming 3 ancestral populations.

Statistical methods

We tested the associations between each SNP and asthma status using logistic regression, adjusting for potential confounders, including global and