# Latino populations: a unique opportunity for epidemiological research of asthma

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## Summary

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Asthma is a significant health problem among Latinos, the largest minority population in the US. Asthma prevalence, morbidity and mortality are highest in Puerto Ricans, intermediate in Dominicans and Cubans, and lowest in Mexicans and Central Americans. From a cultural and social perspective, Latinos represent a wide variety of national origins and ethnic and cultural groups, with a full spectrum of social class. From a genetic perspective, Latinos have descended from Native American, European and African populations. Here, we review results from recent genetic and clinical studies to illustrate the unique opportunity Latino groups offer for studying the interaction between racial, genetic and environmental contributions to asthma and drug responsiveness.

**Keywords:** *asthma*, *ethnic group*, *pharmacogenetics*, *population stratification*, *genetic association*, *gene–environment interaction*.

## Introduction

Latinos Hispanics are the largest, youngest and fastest-growing minority population in the US, accounting for 14% of the nation's total population, and by the year 2050, it is predicted they will comprise 25% of the US population.[1,2] Furthermore, among all US children, Latinos represent the largest demographic group.[3] Asthma is a common respiratory disease of children and adults that is caused by genetic and environmental factors. Its prevalence and severity varies considerably between countries, as well as between different populations within countries.[4,5] According to US vital statistics, asthma prevalence, morbidity and mortality are highest in Puerto Ricans, intermediate in Dominicans and Cubans, and lowest in Mexicans and Central Americans.[6–8] In fact, there is a fourfold difference in asthma prevalence between Puerto Ricans and Mexicans, and population-based surveys in Puerto Rico have confirmed that Puerto Ricans have some of the highest asthma prevalences in the world.[9,10] The discrepancy in asthma burden, as well as the paucity of studies of asthma in Latinos and especially among different Latino ethnic groups, has led the American Academy of Pediatrics to identify asthma among Latinos as an urgent priority for further research.[11]

The term 'Hispanic' or 'Latino' describes a population with a shared cultural heritage and most often a universal language, but does not refer to race or a common ancestry. The two largest Latino ethnic groups in the US, Mexicans (63%) and Puerto Ricans (11%),[2] are genetically complex and composed of various proportions of Native American, African and European genetic origins.[12] Although the relative ancestral contributions to the contemporary Latino gene pool make each Latino national or ethnic group unique, there is substantial overlap in ancestry. Therefore, individuals with similar ancestral proportions may still belong to different Latino ethnic groups. Furthermore, most Latinos are unaware of their precise ancestry and report their ancestry based on the national origin of their family and their physical appearance. The unavailability of precise ancestry and the genetic complexity among Latinos may complicate asthma research in this population due to genetic confounding. On the other hand, precisely because of this complexity, Latinos present a unique opportunity to

 

disentangle the clinical, social, environmental and genetic underpinnings of population differences in asthma prevalence, severity and bronchodilator drug responsiveness.

## Complex genetic diseases in ethnically diverse populations

Complex genetic diseases, such as asthma, cancer, diabetes and atherosclerosis, are likely to be due to multiple, potentially interacting, genes and environmental factors and thus are more challenging to study than simple Mendelian diseases. Presumably, many of these environmental and genetic risk factors are contextual, in that other factors, such as racial background, are likely to be key modifiers of these risk factors. This general phenomenon is referred to as effect modification, and represents an interaction between two or more variables.

One of the best-known examples of a gene that affects a complex disease is *APO-E*. A variant of this gene, *APO-E4*, substantially increases the risk of Alzheimer's disease. *APO-E4* is relatively common and is seen among all racial and ethnic groups, albeit at different frequencies, ranging from 9% in the Japanese population to 14% in Caucasians and to 19% in African Americans.[13] However, a comprehensive meta-analysis demonstrated that the impact of the *APO-E4* on Alzheimer's disease varies by race.[13] Homozygosity for the E4 allele increases risk 33-fold in Japanese, 15-fold in Caucasians, but only 6-fold in African Americans. Although the reason for this variation in risk remains unknown, it suggests potential ethnic-specific genetic and/or environmental modifiers of this gene. Thus, even when a genetic determinant of a complex disease is present in all racial and ethnic groups, racial and ethnic classification may offer additional important insights. Importantly, it is likely that race and ethnicity modify the effect of genetic susceptibility loci (gene–gene interactions) and/or environmental risk factors (gene–environment interactions) for other complex diseases, such as asthma.

The Genetics of Asthma in Latino Americans (GALA) study is a multicentre, international effort designed to identify and directly compare clinical, genetic and environmental risk factors associated with asthma, asthma severity and drug responsiveness among Latino ethnic groups. In our first analysis of GALA participants,[14] we compared asthma-related clinical characteristics among 684 Mexican and Puerto Rican individuals with asthma recruited from San Francisco, New York City, Puerto Rico and Mexico City. We found that Puerto Rican asthmatics had a higher risk of an emergency department visit in the previous year (odds ratio (OR) 2.63 [95% confidence interval (CI) 1.6, 4.3]; $P < 0.001$), and of previous hospitalisation for asthma (OR 1.94 [95% CI 1.2, 3.2]; $P = 0.009$) than Mexicans. We also tested participants for responsiveness to albuterol, a $\beta_2$-adrenergic receptor agonist and bronchodilator drug, by measuring the percentage change from baseline forced expiratory volume in 1 second ($FEV_1$). Worldwide, albuterol is the most commonly prescribed treatment for asthma. Interestingly, Puerto Ricans with asthma had on average 7.3% ([95% CI 4.6, 9.9]; $P < 0.001$) lower bronchodilator responsiveness than Mexicans with asthma. This finding suggests that there may be subgroups of subjects with asthma who may not respond well to commonly prescribed asthma therapies. If replicated, this finding could have important clinical and public health implications.

Despite the ubiquitous use of albuterol in the treatment of asthma, there is significant variation in drug efficacy,[15] as suggested by our finding in Puerto Ricans and Mexicans. Understanding the genetic basis of variability in drug response (pharmacogenetics) will help physicians to optimise their diagnosis and treatment of individual patients or patient groups. Among GALA participants, we demonstrated that there are ethnic-specific genetic factors that contribute to observed differences in physiological response to albuterol. Specifically, we demonstrated that the Arg16 allele of the $\beta_2AR$ gene is associated with greater bronchodilator responsiveness among Puerto Ricans but not Mexicans with asthma.[16] Potential causes of this variation include differences in gene–gene and gene–environment interactions, and ethnic-specific differences in patterns of linkage disequilibrium.

Because these and other Latino ethnic groups represent genetically admixed populations composed of Native American, European and African ancestries, they can self-identify as any race or of mixed race as defined by the US Census. In the 2000 US Census, 97.9% of the non-Latino US population self-identified as one of the five major racial categories. However, 48% of Latinos self-identified as white, 2% as African/African American, 1% as American Indian and 42% as 'some other race'.[3] This demonstrates the complexity of self-identification of this group for epidemiological studies. However, while self-report among Latinos is

 

generally non-specific for determination of ancestry, genetic markers that provide information on ancestry and newly developed statistical methods are making genetic estimation of group and individual ancestry increasingly more accurate.[17–21] Thus, with the use of novel genetic and epidemiological methods, the study of Latino ethnic groups can provide a valuable opportunity to better understand the interactions of race, genetics and environment, and their relationship to asthma.[22]

## Approaches to studying admixed populations

### *Estimation of individual genetic ancestry and regression analyses*

The use of ancestry informative markers (AIM) to estimate genetic ancestry provides two important advantages to the genetic and epidemiological study of admixed populations: (i) it allows ancestry to be entered as a covariate to adjust for population stratification in genetic association studies; and (ii) it enables testing of associations between genetic ancestry and disease-related phenotypes.

Population stratification exists when a population has been formed by admixture of two or more ancestral populations and when admixture proportions vary among individuals. If the risk of disease varies between ancestral populations, then admixture can confound associations of disease with genotypes at any locus where allele frequencies vary between ancestral populations. For example, if disease frequency is significantly higher in one ancestral population, then any allele which is also more frequent in that ancestral group may be associated with the disease.[23,24] Theoretically, if cases and controls are matched by their genetic ancestry, then the confounding due to population stratification should be eliminated.[25] However, in practice, it may not be possible to precisely match genetic ancestry based on self-report, especially in admixed populations where individuals may not be completely aware of their precise ancestry. Thus, specialised statistical methods must be employed to adjust for ancestry and prevent confounding.

For example, we used AIMs to identify and correct for population stratification among Mexican and Puerto Rican subjects participating in case–control studies of asthma.[26] Three hundred and sixty-two subjects with asthma (Mexican: 181, Puerto Rican: 181) and 359 ethnically matched controls (Mexican: 181, Puerto Rican: 178) were genotyped for 44 AIMs. We observed a greater than expected degree of association between pairs of AIMs on different chromosomes in Mexicans ($P < 0.00001$) and Puerto Ricans ($P < 0.00002$) providing evidence for population substructure and/or recent admixture. To assess the effect of population stratification on association studies of asthma, we measured differences in genetic background of cases and controls by comparing allele frequencies of the 44 AIMs. Among Puerto Ricans but not Mexicans, we observed a significant overall difference in allele frequencies between cases and controls ($P = 0.0002$); of 44 AIMs tested, 8 (18%) were significantly associated with asthma. However, after adjustment for individual ancestry, only two of these markers remained significantly associated with the disease, as would be expected by chance (i.e. null hypothesis). Our findings suggest that empirical assessment of the effects of stratification is critical to the appropriate interpretation of the results of case–control studies in admixed populations.

These analyses imply that despite careful study design and recruitment of individuals from the same geographical location and clinics, and with both parents and all four grandparents of the same ethnicity, population stratification can confound genetic association studies of asthma among individuals from admixed populations. Additionally, recent evidence has shown that population stratification can even confound associations with some phenotypes among Caucasians, a population not hitherto considered to be highly admixed.[27]

In addition to serving as a model covariate to control for population stratification, measuring genetic ancestry may provide novel insights into disease aetiology by testing for associations between ancestry and disease-related phenotypes. For example, in a previous study,[12] we used 44 AIMs to first show that Mexicans are generally different from Puerto Ricans in terms of ancestry. While Puerto Ricans as a whole have 66% European ancestry, Mexicans have 45%. Puerto Ricans have 16% African ancestry compared with 3% for Mexicans, and 18% Native American ancestry compared with 52% for Mexicans. Despite these average differences, it is still possible that some individual Mexicans and Puerto Ricans overlap in terms of ancestry because of considerable variation within each group (Fig. 1).

To determine whether the striking differences observed in asthma severity between Puerto Ricans and

 

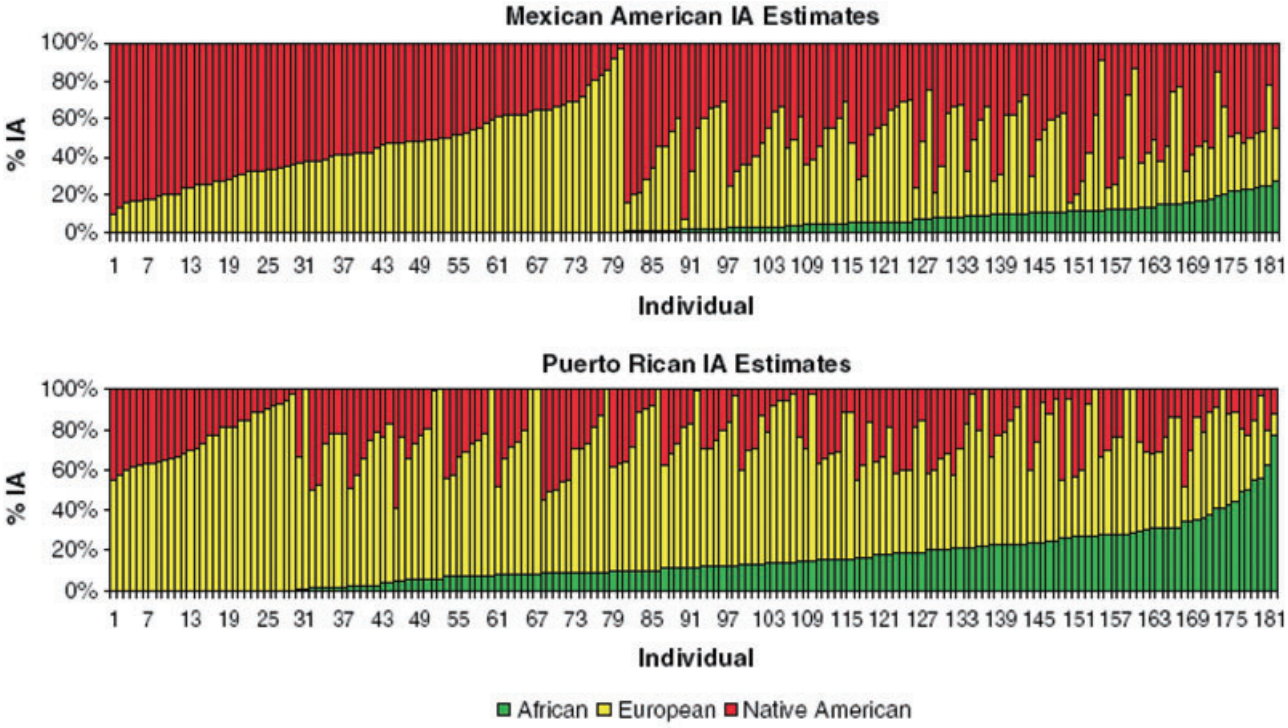


**Figure 1.** Individual ancestry (IA) estimates. Estimates for 181 Mexican American asthmatics (top) and 181 Puerto Rican asthmatics (bottom) are shown, clustered by admixture level. The distribution of IA estimates in Mexican Americans covers the range of European and Native American proportions, while African ancestry contributes very little to this population. However, in Puerto Ricans, African and European ancestries show a high degree of variability, while Native American ancestry exhibits a more restricted pattern of variation. Note that some Mexican and Puerto Rican individuals overlap in terms of ancestry.

Mexicans may be due to the relative differences in ancestral contributions to the contemporary Puerto Rican and Mexican gene pool, we tested the association between asthma-related phenotypes and ancestry in Puerto Rican ($n = 181$) and Mexican ($n = 181$) asthmatics.[12] Using the same 44 AIMs, we estimated individual admixture and found Native American ancestry to be associated with mild asthma whereas European ancestry was associated with severe asthma, defined by lower baseline $FEV_1$ ($P = 0.0051$), after correction for potential confounders. Ancestry was similarly associated with asthma severity, as defined by asthma medication use and clinical symptoms. These associations between ancestry and asthma-related phenotypes provide supporting evidence for the use of admixture-mapping methods to identify genes associated with asthma-related phenotypes among Latino populations.[28]

### *Gene–environment interactions with disease*

Because complex disorders, such as asthma, are probably due to multiple, potentially interacting, genes and environmental factors, they are challenging to study. However, the wide variation in admixture and environmental exposure in Latino ethnic groups provides a unique opportunity to identify novel genetic and environmental risk factors for asthma, as well as to examine gene–environment interactions that can modify disease risk and severity.

One successful example of the identification of a gene–environment interaction modifying asthma resulted from a recent family-based genome-wide screen for asthma susceptibility loci, which revealed linkage with the 5q31 region of chromosome 5, but only among those subjects who were exposed to environmental tobacco smoke (ETS). Among the candidate genes in this region was CD14. The CD14 protein is a pattern-recognition receptor and mediates efficient responses to bacterial lipopolysaccharide (LPS).[29] LPS has been identified as an active component of cigarette smoke,[30,31] and exposure to low concentrations of LPS may trigger immunoglobulin E (IgE)-mediated immune responses important in the immunopathology of asthma.[32] To determine whether genetic variation in the CD14 gene was related to this gene–environment

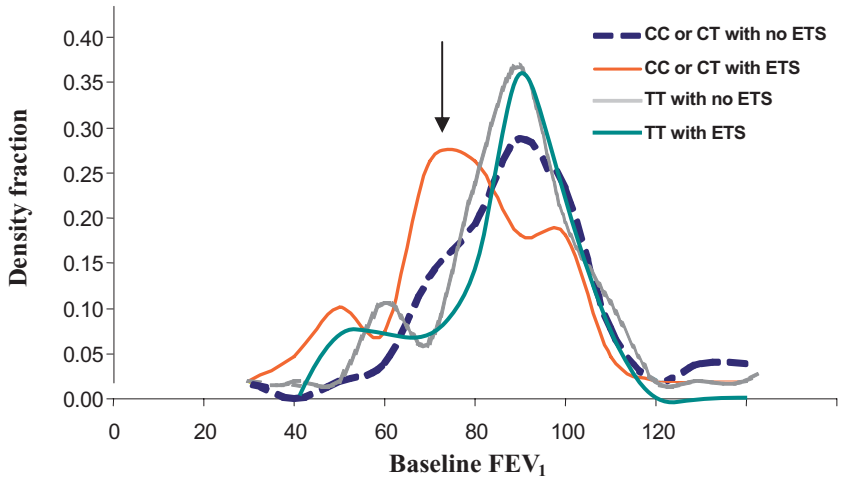


**Figure 2.** Population density plot for deciles of baseline forced expiratory volume in 1 second ($FEV_1$) in Mexican asthmatics stratified by CD14 genotype and environmental tobacco smoke (ETS) exposure. Note that the asthmatics with CC or CT genotype that were exposed to ETS have lower baseline $FEV_1$ than the group not exposed to ETS.

interaction in Latinos, we used both family-based and cross-sectional cohort analysis to test for interactions between CD14 single nucleotide polymorphisms (SNPs) and haplotypes, exposure to ETS and asthma-related phenotypes in 659 Mexican and Puerto Rican families.[33]

To test the possibility of an interaction between CD14 genotypes and ETS and its effect on asthma and asthma-related phenotypes, we stratified families according to whether the asthmatic subject had been exposed to ETS. Among Mexican subjects exposed to ETS, there was a significant association between two genetic variants (SNP −159 and +1437) and baseline $FEV_1$, a quantitative measure of asthma severity ($P = 0.002$ and 0.007 respectively). However, among Puerto Ricans we only observed a significant association for asthma severity with SNP +1437 ($P = 0.04$). As family-based analyses suggested an association between SNP +1437, SNP −159 genotypes, ETS and baseline $FEV_1$, we tested the clinical magnitude of the effect of SNP +1437, SNP −159 genotypes and ETS on baseline $FEV_1$ levels using a cross-sectional study design in Mexican and Puerto Rican asthmatic subjects. Although these results may be susceptible to confounding because they are based on comparison of unrelated individuals, results for this analysis were consistent with the family-based associations in the Mexican and the Puerto Rican populations. There was a significant association when subjects were stratified by +1437 or −159 genotype and ETS exposure. For SNP −159, Mexican asthmatic subjects who carried the CC or CT genotype and who were exposed to ETS had mean baseline $FEV_1$ (83.5 ± 0.43%) values 8.8% lower than subjects who carried the CC or CT genotype and who were not exposed to ETS (92.2 ± 0.35%) ($P = 0.01$; Fig. 2). There was no significant difference in baseline $FEV_1$ levels by ETS exposure in the group with TT genotype ($P = 0.39$). Taken together, these results demonstrate an interaction between exposure to ETS and genetic variants in the CD14 gene that is related to asthma severity. In addition, as previously observed in Caucasians, we also found an interaction between plasma IgE levels, SNP −159 genotypes and ETS exposure ($P = 0.0002$). The lowest IgE levels were in those subjects with the TT genotype and who were exposed to ETS regardless of ethnicity.

In addition to candidate gene–environment interactions, global gene–environment interactions for asthma can be investigated using variables such as ancestry and socio-economic status (SES). Ancestry and SES are likely to be proxies or surrogates for the true genetic and environmental contributing agents. It is well known that within and across racial/ethnic groups, asthma prevalence varies with SES, with higher prevalence observed among low-SES populations.[34,35] In addition to individual SES status, community SES also influences the asthma risk.[36–38] Claudio and colleagues demonstrated that children who live in predominantly low-SES communities had a 70% increased risk of having asthma, independent of ethnicity and individual income level, except for Puerto Rican children, who had high asthma prevalence, regardless of income.[37]

The higher asthma prevalence and morbidity rates experienced by Puerto Rican children cannot be explained by sociodemographic risk factors or other factors assessed in traditional epidemiological surveys.[8] We hypothesised that in this admixed population, the

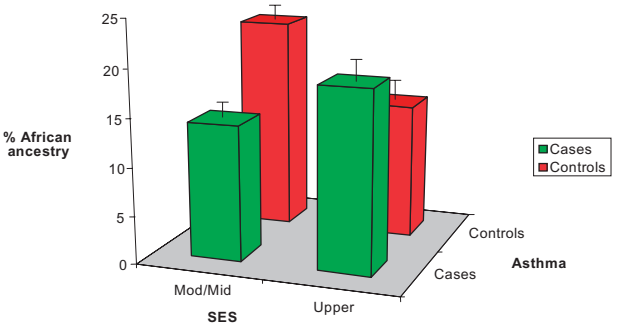


**Figure 3.** Percentage African ancestry in Puerto Rican asthma cases and controls stratified by socio-economic status (SES). SES was obtained using clinic recruitment site address.

association between SES and asthma may interact with genetic ancestry.[39] We estimated individual ancestry using 44 AIMs for 135 Puerto Rican asthma cases and 156 controls recruited from 6 different recruitment centres in Puerto Rico. SES was assigned using the census tracts' median family income. Indeed, we found a significant and complex interaction between SES, ancestry and asthma disease status (Fig. 3). Specifically, among individuals with higher SES, asthma risk increased with African ancestry. In contrast, for those of lower SES, asthma risk increased with European ancestry. Our observations provide an important example for the general discussion of racial/ethnic differences in health and disease experiences.

These observations illustrate the possibility that genetic factors that predispose in one environment (for example, one with greater toxic exposures) may be protective in another environment (for example, one lacking in those exposures). The observed interaction may help to explain the unique pattern of risk for asthma in Puerto Ricans, and the lack of association with SES observed in previous studies when not accounting for varying proportions of ancestry. The results highlight the challenges in capturing the multidimensional risk factors for asthma and their interactions, and underline the need for more comprehensive research that spans the boundaries of traditional research disciplines.

## Conclusions

Asthma is a complex disease that demonstrates variation in prevalence, morbidity and mortality among different ethnic groups, particularly Latinos, with Puerto Ricans exhibiting a fourfold higher disease burden than Mexicans. Additionally, it has been shown that asthma or asthma-related phenotypes are associated with genetic ancestry, and that specific genes as well as genetic ancestry interact with environmental factors to affect asthma phenotypes. These observations strongly suggest that genetic background and environmental factors can modify asthma risk and severity.

From the perspective of clinical and genetic epidemiology, Latinos are a complex and potentially challenging population to study. The recent formation of this population through a complex admixing of ancestral populations has also been shaped by socio-economic, sociopolitical and geographical factors. Great demographic shifts in the Latino population throughout the US and Latin America have compounded the issues of a mixed race, shared culture, unique environments, significant migrations, and continued socio-economic and ethnic discrimination.

Latinos are not a homogeneous ethnic group, as there is great genetic diversity and socio-economic, educational and demographic variation both between and within Latino ethnic groups. This diversity among Latinos provides a unique and valuable opportunity to study the interactions of race, genetics, culture, environment and their impact on asthma. By taking advantage of such diversity, we may gain a much more thorough understanding of asthma, which will benefit all.

Portions of this manuscript also appear in previously published works.[12,14,16,22,26,33,39]

## Conflicts of interest

The authors have declared no conflicts of interest.

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