Ancestry–Environment Interactions and Asthma Risk among Puerto Ricans

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Background: Puerto Ricans, an admixed population of African, European, and Native American ancestries, have the highest asthma prevalence, morbidity, and mortality rates of any United States' population. Although socioeconomic status (SES) is negatively correlated with asthma incidence in most populations, no such relationship has been identified among Puerto Ricans. We hypothesized that, in this admixed population, the association between SES and asthma may interact with genetic ancestry.

Methods: We analyzed 135 Puerto Rican subjects with asthma and 156 control subjects recruited from six different recruitment centers in Puerto Rico. Individual ancestry for each subject was estimated using 44 ancestry informative markers. SES was assigned using the census tracts' median family income. Analyses of SES were based on the SES of the clinic site from which the subjects were recruited and on a subset of individuals on whom home address–based SES was available.

Results: In the two (independent) analyses, we found a significant interaction between SES, ancestry, and asthma disease status. At lower SES, European ancestry was associated with increased risk of asthma, whereas African ancestry was associated with decreased risk. The opposite was true for their higher SES counterparts.

Conclusions: 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.

Keywords: Latino; asthma; admixture; gene-environment; socioeconomic status

Asthma prevalence and severity vary considerably among countries and among different populations within countries (1). Interactions between genetic, environmental, and social factors have been proposed to explain the observed differences in asthma

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Interactions between socioeconomic status and ancestry with respect to asthma among Puerto Ricans have not previously been studied.

What This Study Adds to the Field

Genetic factors that predispose in one environment may be protective in another environment. These results provide an important example for racial/ethnic differences in health and disease experiences.

prevalence (2). However, these interactions are not well understood. For example, the prevalence of asthma in the United States varies with race/ethnicity, a social construct that captures social and biological experiences (3–8). Whites and African Americans exhibit an asthma prevalence of 13 and 16%, respectively, whereas the two largest Latino ethnic groups in the United States, Puerto Ricans and Mexican Americans, have the highest (26%) and lowest (10%) asthma prevalence, respectively (8). Asthma prevalence also varies with socioeconomic status (SES) within and across racial/ethnic groups, with low-SES populations exhibiting higher rates (9, 10). In addition to individual SES status, neighborhood SES influences the risk of asthma (5, 11, 12). Claudio and colleagues demonstrated that children who live in predominantly low-SES communities had a 70% increased risk of current asthma, independent of ethnicity and individual income level, except for Puerto Rican children, who had high asthma prevalence regardless of income (12).

The higher asthma prevalence and morbidity rates experienced by Puerto Rican children cannot be explained by traditional measures of sociodemographic and other risk factors assessed in traditional epidemiologic surveys (8). The Puerto Rican population is genetically complex and is descended from the recent admixing of three ancestral populations (Native American, European, and African) (13). Although ecologic studies focus on self-identified race and ethnicity, with the advent of ancestry informative genetic markers (AIMs), it is possible to examine the association between disease or trait frequency and individual ancestry estimates (13–15). Thus, within the Puerto Rican population, AIMs afford the opportunity to study the complex interaction between individual ancestry, SES, and asthma.

METHODS

Study Participants

Puerto Rican subjects with asthma were recruited as part of the ongoing Genetics of Asthma in Latino Americans Study (16–18). Briefly, a total

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of 135 subjects with asthma and 156 control subjects were ascertained through six primary care clinics in Puerto Rico: Barceloneta, Bayamon, Carolina, Cataño, Mayagüez, and San Juan. Subjects were eligible to participate if they were between the ages of 8 and 40 yr and had physician-diagnosed asthma and two or more asthma symptoms (e.g., wheezing, coughing, and shortness of breath) in the last 2 yr. Control subjects were screened from the same clinics and considered to be eligible to participate if they did not have a smoking history, clinical evidence of asthma, allergies, atopy, or any other allergic or pulmonary disease and were between the ages of 8 and 40 yr. All subjects were interviewed by bilingual and bicultural field workers and physicians specializing in asthma. All subjects were recruited from the six clinics by the same investigators using similar recruitment criteria. Clinical assessments of affected subjects were performed, including measures of FEV₁, which confirmed the diagnosis of asthma.

SES

The Federal Financial Institutions Examination Council's (FFIEC) Geocoding/Mapping System (<http://www.ffiec.gov/geocode/default.htm>) was used as a proxy for SES. The FFIEC classifies subjects into one of four U.S. Census 2000 tract income levels: low, moderate, middle, and upper. This classification is based on the census tract's median family income (MFI) divided by the MFI of the metropolitan area (MA MFI) that the tract is located in, or MFI %. If the MFI % is less than 50, then the income level is classified as "low"; if the MFI % is ≥ 50 and < 80 , then the income level is classified as "moderate"; if the MFI % is ≥ 80 and < 120 , then the income level is classified as "middle"; and if the MFI % is ≥ 120 , then the income level is classified as "upper." SES was assigned to individuals based on clinic recruitment site address (available for the entire sample) and the subject's home address, which was available for 38 cases and 109 control subjects.

Classification of Latino Subgroup

Ethnicity and national origin were self-reported and were ascertained based on standardized questions. Subjects were enrolled only if both biological parents and all four biological grandparents were reported to be of Puerto Rican origin. Interviews with children were conducted in the presence of their biological parents. Institutional review boards at the University of Puerto Rico, San Juan, and the University California, San Francisco, approved all studies, and all subjects provided written, age-appropriate informed consent or assent.

Marker Selection and Genotyping

Individual ancestry estimates were determined based on genotyping data from 44 autosomal AIMs in all Puerto Rican study subjects. The method of genotyping and primer sequences for the markers has been described previously (14, 15, 19, 20).

Statistical Analysis

Individual ancestry (IA) estimates were derived using the program STRUCTURE 2.1 (<http://pritch.bsd.uchicago.edu>) (21). STRUCTURE was run under an admixture model with default values for other parameters, with 50,000 burn-in iterations and 50,000 further iterations, as suggested by the authors. IA estimates were also produced using a frequentist approach as described by Tang and colleagues (22), and the estimates obtained using frequentist and STRUCTURE estimates were found to be highly correlated with respect to all three ancestry components ($r^2 > 0.9$). Analysis of variance (ANOVA) with IA estimate (% African or European or Native American) as a continuous outcome was used to examine the association between asthma disease status and individual ancestry adjusted for age, sex, and clinic recruitment site. If necessary, the IA estimates were square root transformed to make them more normally distributed. To determine whether the association between asthma disease status and ancestry varies with SES, SES and an interaction term between SES and disease status were included in the ANOVA. In the ANOVA analyses, two SES groups were defined: those with moderate or middle SES and those with upper SES. The moderate and middle groups were combined because of small numbers for the moderate group. In the ANOVA analysis focusing on residence-based SES, two interaction terms were included: one for residence-based SES and disease status and one for recruitment-site SES and disease status. We included the latter term to determine the interaction

effect of residence-based SES independent of recruitment-site SES. ANOVA analyses were performed with the statistical software program STATA 8.0 (StataCorp LP, College Station, TX).

RESULTS

Subject Characteristics

Overall, Puerto Rican subjects with asthma (age, 15.6 ± 8.2 yr) were significantly younger than control subjects (age, 25.9 ± 9.8 yr; $p = 0.0001$). The proportion of male subjects was higher in control groups (51.9%) than in cases (28.0%; $p = 0.0001$).

Comparison of Cases and Control Subjects by Ancestry Proportions and SES

Overall, subjects with asthma had less African ancestry and greater European ancestry than healthy control subjects (Table 1). There was no difference in Native American ancestry between cases and control subjects. Because the cases and control subjects were significantly imbalanced with respect to age and sex, we were concerned that either or both of these factors could confound further analyses examining ancestry, SES, and asthma. However, there was no difference in ancestry proportions between male and female subjects for any of the ancestral groups, and the correlations between the ancestry proportions and age were uniformly small and nonsignificant (Table 2).

Because admixture proportions may vary among subjects who are ascertained at different clinic recruitment sites, we compared admixture proportions between cases and control subjects by clinic recruitment site and SES. These analyses found differences between cases and control subjects in African and European but not Native American ancestral proportions by clinic recruitment site (Table 1). However, the relationship was complex. Among the control subjects from the clinic recruitment sites with lower SES (Barceloneta, Cataño, and Mayagüez), African ancestry was increased and European ancestry decreased compared with healthy control subjects from the clinic recruitment sites with higher SES (San Juan, Bayamon, and Carolina). The opposite trend was observed for the subjects with asthma: Among the cases from clinic recruitment sites with lower SES, African ancestry was decreased, whereas European ancestry was increased, compared with cases from recruitment sites with high SES (Figure 1). No such interaction was observed for Native American ancestry.

Results from the ANOVA of ancestry confirmed the SES–ancestry interaction. None of the main effects alone (recruitment site, recruitment site SES, sex, age, and case-control status) was statistically significant, but the interaction term between recruitment site SES and case-control status was significant for African ancestry (p value for interaction, 0.005) and European ancestry ($p = 0.028$; Table 2).

Because we found substantial differences in ancestry between asthma cases and healthy control subjects by SES in the analysis of all subjects using clinic recruitment site SES, we performed a similar analysis using home address–based SES within the two clinic recruitment sites that had such information on cases and control subjects (Cataño and San Juan). This analysis was possible because within these clinic recruitment sites there was variation in home address–based SES among the recruited subjects. Therefore, these data provided an opportunity for independent replication at the finer level of individual SES of what we had observed at the crude level of group SES defined by the clinic recruitment site SES.

In this analysis, our previous results were clearly replicated, even in this reduced sample, and the effect sizes were increased (Table 3). Specifically, within recruitment site, asthma cases of lower SES exhibited less African ancestry and greater European

TABLE 1. AFRICAN, EUROPEAN, AND NATIVE AMERICAN ANCESTRY AMONG CASES WITH ASTHMA AND CONTROL SUBJECTS BY CLINIC RECRUITMENT SITE SOCIOECONOMIC STATUS

Clinic Recruitment Site	SES	n (case/control)	African			European			Native American		
			Case	Control	δ^*	Case	Control	δ	Case	Control	δ
Barceloneta	Moderate	23/3	10.0 $\pm$ 8.3	8.0 $\pm$ 5.3	2.0	70.2 $\pm$ 15.8	68.0 $\pm$ 7.0	2.2	19.8 $\pm$ 12.7	24.0 $\pm$ 4.6	-4.2
Cataño	Middle	37/81	19.6 $\pm$ 14.5	24.1 $\pm$ 15.9	-4.5	59.3 $\pm$ 14.5	56.2 $\pm$ 18.7	3.1	21.1 $\pm$ 13.8	19.7 $\pm$ 16.1	1.4
Mayagüez	Middle	13/34	7.1 $\pm$ 6.8	18.9 $\pm$ 15.8	-11.8	72.1 $\pm$ 13.4	60.3 $\pm$ 18.4	11.8	20.8 $\pm$ 10.5	20.8 $\pm$ 14.1	0.0
All _{Mod/Mid}	Mod/Mid	73/118	14.2 $\pm$ 12.7	22.2 $\pm$ 16.0	-5.9	65.2 $\pm$ 15.6	57.7 $\pm$ 18.5	5.3	20.7 $\pm$ 12.8	20.1 $\pm$ 15.3	-0.6
San Juan	Upper	38/29	20.2 $\pm$ 18.4	13.3 $\pm$ 12.6	6.9	62.4 $\pm$ 21.2	68.7 $\pm$ 13.9	-6.3	17.4 $\pm$ 14.3	18.0 $\pm$ 10.8	-0.6
Bayamon	Upper	12/7	19.7 $\pm$ 14.4	13.9 $\pm$ 11.3	5.8	60.4 $\pm$ 16.4	73.4 $\pm$ 8.8	-13.0	19.9 $\pm$ 13.8	12.7 $\pm$ 4.7	7.2
Carolina	Upper	12/2	14.6 $\pm$ 11.0	27.5 $\pm$ 9.2	-12.9	64.9 $\pm$ 15.5	34.5 $\pm$ 30.4	30.4	20.5 $\pm$ 18.1	30.0 $\pm$ 39.6	-17.5
All _{Upper}	Upper	62/38	19.0 $\pm$ 16.4	14.2 $\pm$ 12.4	5.2	62.5 $\pm$ 19.1	67.8 $\pm$ 15.8	-4.8	18.6 $\pm$ 14.0	18.1 $\pm$ 12.7	-0.4
All	All	135/156	16.4 $\pm$ 14.7	20.2 $\pm$ 15.5		63.9 $\pm$ 17.3	60.2 $\pm$ 18.3		19.7 $\pm$ 13.7	19.6 $\pm$ 14.7	

Definition of abbreviation: SES = socioeconomic status.

* δ represents the difference in ancestry proportion between cases and control subjects.

ancestry compared with lower SES control subjects, whereas cases of higher SES had greater African ancestry and less European ancestry compared with the higher SES control subjects. There were no differences in Native American ancestry. Results of the ANOVA based on the data of Table 3 demonstrated a statistically significant interaction between home address SES and disease status, in the same direction as previously found using recruitment site SES on the full sample, for African ancestry ($p = 0.021$) and European ancestry ($p = 0.014$) but not Native American ancestry (Table 4). This interaction persisted after allowing for an interaction between disease status and recruitment site (in this case equivalent to recruitment site SES because there were only two sites included, one of middle SES and the other of upper SES). Although the two SES measures (based on clinic site and home address) are correlated, in this analysis the effect of the interaction of home address-based SES and disease status is examined after controlling for the originally observed effect of clinic-based SES and disease status interaction. In this analysis, ancestry is compared between residence-based SES categories within clinic sites. Thus, the observed effect for residence-based SES is statistically independent of the one first observed for clinic site.

To address the question of potential selection bias, whereby SES and/or ancestry influenced clinic attendance, we examined an objective measure of asthma (FEV_1) to determine if it varied with SES (clinic-based and residence-based) or with ancestry (African, European, or Native American). For clinic-based SES, FEV_1 values (mean $\pm$ SD) were 84.5 ± 2.6 (moderate SES, $n = 23$), 85.1 ± 2.1 (middle SES, $n = 50$), and 84.4 ± 2.1 (upper SES, $n = 60$). These values are not statistically different by ANOVA analysis ($p > 0.05$). For residence-based SES, FEV_1 values were 86.2 ± 2.5 (moderate SES, $n = 33$), 85.6 ± 2.9 (middle SES, $n = 18$), and 87.8 ± 3.1 (upper SES, $n = 9$). These values are not statistically different from each other by ANOVA analysis ($p > 0.05$). Finally, we calculated correlations between

FEV_1 and African, European, and Native American IA. These correlations are -0.06 , $+0.01$, and $+0.05$, respectively. None is statistically different from 0. Hence, there seems to be no objective relationship between asthma severity and SES or ancestry in this sample.

DISCUSSION

Our results reveal a complex interaction between SES and ancestry with respect to asthma within the Puerto Rican population. Among individuals with higher SES, asthma risk increased with African ancestry. By contrast, for those of lower SES, asthma risk increased with European ancestry. Few studies have focused on gene-environment interactions in humans (2). Although we have previously demonstrated gene-environment interactions for asthma in Latino populations where the environmental exposure is second hand tobacco smoke (23), the results reported here reflect a more global interaction between ancestry (possibly reflecting genetic background), SES, and asthma, suggesting the complexity of the gene-environment interaction for asthma. To our knowledge, this is the first demonstration of an interaction between ancestral proportions, environmental factors, and the risk of asthma or any complex disease.

For this analysis, we used a measure of SES based on the median family income of the subject's home address and of the clinic recruitment site address from which the subject was recruited. SES is a complex multidimensional construct that captures many variables, including unmeasured environmental factors (24). Income, education, and job position are some of the proxy variables used to measure SES. The health-related effects of SES are mediated directly by hazardous exposures or indirectly by influencing health behaviors and access to and quality of health care (25). SES has been described as operating at different levels (i.e., individual, household, and neighborhood); socioeconomic factors can interact with social experiences and

TABLE 2. RESULTS OF ANOVA ON ANCESTRY FOR RECRUITMENT SITE SOCIOECONOMIC STATUS

Variable	df	African		European		Native American	
		F	p Value	F	p Value	F	p Value
Disease status	1	0.06	0.802	0.01	0.910	0.01	0.905
Recruitment site	4	3.27	0.012	2.22	0.067	0.44	0.779
SES _{recruitment site}	1	0.82	0.367	0.03	0.861	1.29	0.256
Disease $\times$ SES _{recruitment site}	1	8.21	0.005	4.85	0.028	0.06	0.808

Definition of abbreviations: df = degrees of freedom; SES = socioeconomic status.

Figure 1. Percentage of African ancestry in Puerto Rican cases with asthma and control subjects stratified by socioeconomic status (SES). SES was obtained using clinic recruitment site address.

characteristics such as racial/ethnic group and sex to produce different health effects across groups (24). Furthermore, factors determined by SES can be time sensitive in that they could have different effects on the causal pathway depending on when they occurred in the life course (i.e., childhood vs. adulthood). In addition, an individual's health can be affected not only by the socioeconomic characteristics of the household but also the neighborhood in which the individual lives (25–28). The effects of neighborhood SES could be mediated through different causal pathways including the physical (i.e., built), social, or service environment. One pathway by which SES can influence health is through the production of high allostatic load, which leads to a variety of deleterious health and cognitive outcomes (29). SES may change allostatic response through environmental factors, such as levels and types of indoor home allergens, smoking, pests, and exposure to outdoor pollution, all of which are critical to asthma risk (30, 31).

Although our results are internally consistent, they are tempered by several caveats. First, we did not have individual SES data from early life, and we did not have information on how long subjects lived in a given location. The lack of this information may limit our ability to measure the effects of events that happened in the early stages of life, depending on the degree of mobility in this population. It is also possible that there was misclassification. If nondifferential misclassification occurred, then the results presented here could be underestimates of the true effect of SES and ancestry on risk of asthma. Differential misclassification due to systematic differences in recruitment at the various clinic sites could yield false results. For this to occur, however, there would have to be differences in recruitment that biased the ancestry of individuals of high SES groups in one

direction while biasing the ancestry of individuals of low SES groups in the opposite direction. Although this is possible, it is unlikely given that recruitment was standardized and performed by the same recruitment team at all sites. Furthermore, an examination of a subset of data, in which SES was estimated using subject's home address, independently confirmed our initial results based on clinic recruitment site SES. This nested analysis using subject's home address SES within each recruitment site provided results in the same direction, suggesting that the results are unlikely due to chance. Although there is a possibility of variation in family income within census tracts, this variation would bias our results toward the null.

Additional limitations include the imbalance between the number, age, and sex of cases with asthma and control subjects from different recruitment sites and the relatively limited sample size. However, our analyses did control for recruitment site differences, and the results remained robust. Furthermore, age and sex were not associated with ancestry and therefore are unlikely to confound the interaction between ancestry and SES and were also controlled for in the statistical analyses. Finally, it is possible that geographic differences correlate with environmental factors (e.g., climate, pollution, and airborne antigens such as fungal spores) that were not accounted for in our study, although these are likely to operate in a regional way that would have been controlled by our inclusion of recruitment site as a covariate. We analyzed only 44 ancestry informative markers; therefore, individual ancestry was estimated with a degree of statistical noise. However, such noise is nondirectional and would have biased our results toward the null. We would therefore predict that genotyping of additional ancestry informative markers in

TABLE 3. AFRICAN, EUROPEAN, AND NATIVE AMERICAN ANCESTRY FOR CASES WITH ASTHMA AND CONTROL SUBJECTS WITHIN CLINIC RECRUITMENT SITE BY HOME ADDRESS SOCIOECONOMIC STATUS

Clinic Recruitment Site	Home Address SES	n (case/control)	African			European			Native American		
			Case	Control	δ^*	Case	Control	δ	Case	Control	δ
Cataño	Mod/Mid	23/71	17.0 ± 14.2	25.1 ± 13.4	–8.1	61.8 ± 16.3	55.0 ± 18.3	6.8	21.2 ± 12.1	19.9 ± 16.0	1.3
	Upper	6/9	26.3 ± 19.7	12.7 ± 9.2	13.6	55.3 ± 17.2	68.0 ± 17.6	–12.7	18.3 ± 18.1	19.3 ± 14.5	–1.0
San Juan	Mod/Mid	8/6	17.4 ± 10.8	21.0 ± 13.5	–3.6	66.9 ± 19.1	60.8 ± 9.1	6.1	15.7 ± 15.5	18.2 ± 12.6	–2.5
	Upper	2/22	9.5 ± 9.2	11.9 ± 11.8	–2.4	52.5 ± 3.5	70.6 ± 14.7	–18.1	38.0 ± 5.7	17.5 ± 10.7	20.5

Definition of abbreviation: SES= socioeconomic status.

* δ represents the difference in ancestry proportion between cases and control subjects.

TABLE 4. RESULTS OF ANOVA ON ANCESTRY FOR HOME ADDRESS SOCIOECONOMIC STATUS

Variable	df	African		European		Native American	
		F	p Value	F	p Value	F	p Value
Disease status	1	0.04	0.848	0.68	0.411	0.55	0.458
Recruitment site	1	0.67	0.413	0.96	0.329	0.10	0.755
SES _{home address}	1	0.81	0.369	0.18	0.676	0.16	0.694
Disease × recruitment site	1	0.01	0.905	0.01	0.934	0.04	0.835
Disease × SES _{home address}	1	5.47	0.021	6.26	0.014	0.32	0.570

For definition of abbreviations, see Table 2.

this sample would strengthen the patterns of association that we observed here.

The historically observed differential pattern of asthma prevalence across ethnic groups is not consistent with a simple linear trend in terms of the degree of ancestry from any of the ancestral populations. The fact that the highest and lowest asthma prevalence is observed in two Latino populations, with blacks and whites having intermediate prevalence, confounds a simple explanation based on genetics or SES for these differences. One possible explanation involves an intricate interplay between genetic susceptibility, differentially represented in the ancestral populations, with complex environmental triggers, correlated with SES. In this case, it seems from our analyses that the relevant ancestral contributions are from Europe and Africa rather than the Americas. Because in Puerto Ricans the individual ancestries from Europe and Africa are highly negatively correlated, in our study it was impossible to say which of the two is the dominant factor. Mexicans tend to have lower levels of African ancestry compared with Puerto Ricans, although for both the averages are considerably less than 50%. By contrast, African Americans have on average 80% African ancestry. Therefore, it is likely that asthma risk does not track linearly with degree of African ancestry, possibly even in a lower SES environment. Further study of a variety of ethnic groups, incorporating finer measures of SES and ancestry, is required to resolve this paradox. Nonetheless, our observations provide an important example for the general discussion of racial/ethnic differences in health and disease experiences. They illustrate the possibility that genetic factors that predispose in one environment (e.g., one with greater toxic exposures) may be protective in another environment (e.g., one lacking in those exposures).

Although we have shown a statistically significant interaction between ancestry and SES on asthma susceptibility in two independent analyses, our findings should be regarded as preliminary and require replication in a larger study population including locales outside of Puerto Rico. However, these data are important because they provide a new direction for future research. The results presented herein highlight the challenges in capturing the multidimensional risk factors for asthma and their interactions and underscore the need for more comprehensive research that spans the boundaries of traditional research disciplines. The variables we used (SES, ancestry) were only surrogates for the true contributing agents, both environmental and genetic. Future research should focus on identifying those specific factors and their complex interactions as they relate to disease.

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