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Genetic Ancestry Influences Asthma Susceptibility and Lung Function Among Latinos

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Abstract

Background—Childhood asthma prevalence and morbidity varies among Latinos in the United States, with Puerto Ricans having the highest and Mexicans the lowest.

Objective—To determine whether genetic ancestry is associated with the odds of asthma among Latinos, and secondarily whether genetic ancestry is associated with lung function among Latino children.

Methods—We analyzed 5,493 Latinos with and without asthma from three independent studies. For each participant we estimated the proportion of African, European, and Native American ancestry using genome-wide data. We tested whether genetic ancestry was associated with the presence of asthma and lung function among subjects with and without asthma. Odds ratios (OR) and effect sizes were assessed for every 20% increase in each ancestry.

Results—Native American ancestry was associated with lower odds of asthma (OR=0.72, 95% confidence interval [CI]: 0.66–0.78, $p=8.0\times10^{-15}$), while African ancestry was associated with higher odds of asthma (OR=1.40, 95%CI: 1.14–1.72, $p=0.001$). These associations were robust to adjustment for covariates related to early life exposures, air pollution and socioeconomic status. Among children with asthma, African ancestry was associated with lower lung function, including both pre- and post-bronchodilator measures of forced expiratory volume in the first second (−77±19 ml, $p=5.8\times10^{-5}$ and −83±19 ml, $p=1.1\times10^{-5}$, respectively) and forced vital capacity (−100±21 ml, $p=2.7\times10^{-6}$ and −107±22 ml, $p=1.0\times10^{-6}$, respectively).

Conclusion—Differences in the proportions of genetic ancestry can partially explain disparities in asthma susceptibility and lung function among Latinos.

Keywords

genetic admixture; childhood asthma; Hispanics; minority; pulmonary function

Introduction

There are significant differences in asthma prevalence and morbidity among racial/ethnic minority children in the U.S.[1] Asthma prevalence is highest in Puerto Ricans (18.4%), followed by African Americans (14.6%), European Americans (8.2%), and Mexican Americans (4.8%).[2,3] Moreover, asthma mortality is 4-fold higher in Puerto Ricans as compared with Mexican Americans.[4] While differences in socioeconomic and environmental factors play an important role, they cannot fully explain these disparities.[5] Indeed, familial clustering and twin studies support an important genetic contribution to disease predisposition, with an estimated heritability between 75% and 92%.[6,7] Therefore, genetic factors may play an important role in the variability of asthma prevalence and severity in Latino populations.[8–10]

Although Latino populations are classified as a single ethnic group in the U.S., there is considerable heterogeneity in the proportions of African, European, and Native American genetic ancestry.[11,12] Since the frequency and composition of genetic variants are known to differ between continental populations,[13,14] the variation in the proportions of ancestry may explain the differences observed in the frequencies of genetic risk factors for diseases such as asthma.[8,15] In fact, among African Americans and African Caribbeans, higher levels of African ancestry has been associated with increased susceptibility to asthma and asthma-related traits,[16–20] including lower lung function[21] and increased risk of asthma exacerbations.[22] In Latino children, African ancestry has been negatively correlated with lung function in Puerto Ricans,[23] while Native American ancestry has been associated with higher lung function in Mexican American children with asthma and in adult Costa Ricans.[9,24] Although environmental factors are important in the differences in asthma prevalence,[25,26] we hypothesized that the genetic ancestry can also contribute to the variation observed in asthma prevalence in Latinos . We tested for an association between genetic ancestry and the odds of asthma among 5,493 Latino children with and without asthma from three studies: the Genes-environments & Admixture in Latino Americans (GALA II) study for discovery, and the Genetics of Asthma in Latino Americans study (GALA I) and the Children's Health Study (CHS) for replication. For children from GALA II, we secondarily tested the association between genetic ancestry and lung function.

Methods

Study subjects from GALA II

The GALA II study is an ongoing multicenter case-control study of asthma in Latino children and adolescents.[26] Cases and healthy controls were recruited using a combination of community and clinic-based recruitment from 5 urban study centers throughout the U.S.

(Chicago, Bronx, Houston, San Francisco Bay Area and Puerto Rico). Subjects were eligible if they were 8–21 years of age, self-identified all four grandparents as Latino, and had <10 pack-years of smoking history. Subjects were classified into three Latino ethnicity categories according to the self-reported ethnicity of their four grandparents: Puerto Rican, Mexican American and other Latino (South American, Central American, non-Puerto Rican Caribbean, or mixed Latino).

Asthma was defined based on physician diagnosis and report of symptoms and medication use within the last 2 years. Controls had no reported history of asthma or allergies, and no reported symptoms of wheezing or shortness of breath during their lifetime. All local institutional review boards approved the study and all subjects/parents provided written consent. Detailed clinical measurements, demographic and general health data were recorded for each individual. Pulmonary function testing was conducted according to American Thoracic Society recommendations[27] to obtain standard measurements of airway obstruction, including forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), and forced expiratory flow between 25–75% of vital capacity ($FEF_{25–75}$).

GALA II subjects were genotyped using the Axiom LAT1 array (World Array 4, Affymetrix, Santa Clara, CA).[15,28] After quality control, 3,774 samples were available for the analysis, including Puerto Ricans (n=1,800), Mexicans (n=1,285) and other Latinos (n=689). Further information can be found in the Supplementary Methods in the Online Repository.

Replication Studies

The Genetics of Asthma in Latino Americans study (GALA I) includes children with asthma and their biological parents recruited from the San Francisco Bay Area, New York City, Puerto Rico, and Mexico City.[29] Subjects were included in the study if they were between 8–40 years of age, had physician-diagnosed mild to moderate-to-severe asthma, had experienced 2 or more symptoms in the previous 2 years at the time of recruitment (wheezing, coughing, and/or shortness of breath), and self-identified all 4 grandparents as Puerto Rican or Mexican. Healthy controls who reported all four grandparents as Puerto Rican or Mexican were recruited from the same sites as asthma cases in the San Francisco Bay Area and Puerto Rico. In the current study, only Mexicans Americans recruited in the San Francisco Bay Area were included in the analysis (170 cases and 151 controls), as Puerto Ricans were part of a previous study.[30] All subjects were genotyped on the Affymetrix 6.0 GeneChip.[10]

The Children’s Health Study (CHS) is a cohort study investigating both genetic and environmental factors related to childhood asthma and lung function in southern California. Based on questionnaire responses, a nested case-control sample of children having physician diagnosed asthma at study entry or during active follow-up (cases) and children never having a diagnosis of asthma (controls) was selected for genotyping on the HumanHap550, HumanHap550-Duo or Human610-Quad BeadChip microarrays (Illumina, San Diego, CA), as described elsewhere.[31] Only individuals self-identified as Hispanic white were included as part of the current study (606 cases and 792 controls).

More details on genotyping and quality control procedures for each study are given in the Online Repository Text.

Assessment of genetic ancestry

Estimates of African, European and Native American ancestries were obtained for each participant using an unsupervised analysis in ADMIXTURE[32] assuming 3 ancestral populations. We used reference haplotypes from European and African individuals from HapMap phase II,[14] and 71 Native American individuals genotyped on the Axiom LAT1 array.[15] A set of 20,669 SNPs that were common among GALA II, GALA I, CHS, and the reference populations were used for ancestry estimation after removing C/G and A/T SNPs and SNPs potentially in linkage disequilibrium (R^2>0.15). Ancestry estimates were also compared to those obtained using an independent method[33] and showed a high concordance (R^2>0.995, Figure E1). Additionally, principal component analysis (PCA) was performed to compare the samples analyzed in each study.[34] For more details see the Online Repository Text.

Statistical analysis

We tested for an association between African, European and Native American ancestry and the odds of asthma in GALA II using logistic regressions models for each ancestry, stratifying by three Latino ethnicity categories (Mexicans, Puerto Ricans, and other Latinos). These analyses included recruitment region (Puerto Rico, New York, Chicago, Texas, and San Francisco Bay Area), age, and sex as covariates. The analyses of the other Latino group also included the self-reported ethnicity subgroup as a covariate. Other potential covariates were considered in secondary multivariate models if they were associated with asthma in univariate models for each Latino group (Table E1). These potential confounders included: body mass index (BMI) percentiles, preterm birth (born before 37 weeks of pregnancy), number of siblings, daycare attendance in the first 3 years of life, firstborn (yes/no), having pets in the home in the first year of life, exposure to secondhand smoke exposure in three different periods of life (*in utero*, in the first 2 years of life from household smokers, and current from adult household smokers), exposure to air pollutants, and variables related to socioeconomic status (SES: annual household income and mother's highest education level), health care access, discrimination, and acculturation. However, only covariates associated with asthma at *p*-value≤0.05 in the multivariate models for each Latino subgroup were kept in the final models. See the Supplementary Methods in the Online Repository for further detail.

Replication of the association between African, European, and Native American ancestry and asthma was performed in GALA I and CHS using logistic regression adjusting for age and sex.

Lung function measures of FEV_1 and FVC among children with asthma from GALA II were compared across the three Latino ethnicities using linear regression models. We then assessed the association of genetic ancestry with lung function (pre-bronchodilator and post-bronchodilator FEV_1, FVC and $FEF_{25–75}$). All models of lung function included recruitment region, age, sex, height, height^2, and use of controller medication as covariates. In addition,

age at asthma onset was considered as a confounder, but not included in the final regression models as it was not significantly associated with measurements of FEV_1, FVC or $FEF_{25–75}$. We used measured FEV_1 and FVC instead of percent predicted values due to the lack of reference equations for Puerto Ricans.

We also evaluated whether genetic ancestry was associated with lung function among healthy controls that had performed pulmonary function testing (404 individuals: 220 Mexicans, 126 Puerto Ricans, and 58 other Latinos). Given the small sample size, we analyzed all controls combined and adjusted the models by ethnicity, in addition to recruitment region, age, sex, height, and height^2.

Meta-analyses were performed across Mexican Americans, Puerto Ricans and other Latinos from GALA II using fixed effects models or random effect models, if heterogeneity was detected ($p \leq 0.05$), to estimate the overall effect size of ancestry on lung function in Latinos. Odds ratios (OR), 95% confidence intervals (CI), and effect sizes were assessed for every 20% increase in ancestry. All statistical analyses were performed using R version 2.15.

To account for the multiple comparisons performed we adopted a Bonferroni correction. For asthma we analyzed 15 tests, therefore the Bonferroni correction threshold was $\alpha = 3.3 \times 10^{-3}$. For lung function we tested 54 different tests obtaining a corrected threshold of significance of $\alpha = 9.3 \times 10^{-4}$. Post-hoc power calculations were performed with the software Quanto (http://biostats.usc.edu/Quanto.html).

Results

Association of genetic ancestry with asthma susceptibility

Characteristics of the participants included in this study are shown in Table E1 for GALA II and in Table E2 for CHS and GALA I. The distribution of genetic ancestry proportions among individuals is shown in Figure E2 and Table E3 in the Online Repository. PCA showed how genetic data recapitulates reported ethnic classification of Mexican and Puerto Ricans into two clear distinct subgroups of Latinos. However, the category Other Latino represents a more heterogeneous group, with some individuals being closer to the Mexicans than to the Puerto Ricans and vice versa (Figure E3).

For GALA II we found a significantly lower proportion of Native American ancestry in children with asthma as compared with healthy controls in Mexican Americans (OR=0.70, 95%CI: 0.60–0.82, $p = 9.6 \times 10^{-6}$) and a nominal association in other Latinos (OR=0.73, 95%CI: 0.57–0.92, $p=0.008$), but not in Puerto Ricans ($p=0.377$). African ancestry was higher in children with asthma as compared with healthy controls both in Puerto Ricans (OR=1.29, 95%CI: 1.07–1.56, $p=0.007$) and other Latinos (OR=1.62, 95%CI: 1.14–2.30, $p=0.008$) (Table 1), although it was not significant following a Bonferroni correction. European ancestry was associated with higher odds of asthma in Mexican Americans (OR=1.44, 95%CI: 1.22–1.70, $p = 1.5 \times 10^{-5}$), but with lower odds of asthma in Puerto Ricans (OR=0.74, 95%CI: 0.61–0.89, $p=0.002$). The association of genetic ancestry with asthma susceptibility was robust to adjustment by SES factors and early life exposures (Table E4).

Native American ancestry was also associated with lower odds of asthma in GALA I and CHS combined (OR=0.71, 95%CI: 0.64–0.79, meta-analysis $p=1.8\times10^{-10}$), although the association was not significant in GALA I alone ($p=0.759$, Table 1). European ancestry was associated with increased odds of asthma in the replication studies (OR=1.34, 95%CI: 1.21–1.47, meta-$p=8.5\times10^{-9}$), consistent with our observations in Mexican Americans in GALA II.

A meta-analysis across all three studies (2,669 cases and 2,824 controls) confirmed a consistent strong association of Native American ancestry with lower odds of asthma (OR=0.72, 95%CI: 0.66–0.78, meta-$p=1.5\times10^{-15}$). Furthermore, African ancestry was associated with higher odds of asthma across all three studies combined (OR=1.40 for each 20% increment in African ancestry, 95%CI: 1.14–1.72, meta-$p=0.001$), but not European ancestry (Table 1).

Association of genetic ancestry with lung function

In GALA II children with asthma, pre- and post-bronchodilator measurements of FEV_1 and FVC were significantly lower in Puerto Rican and other Latino as compared with Mexican American children (Table 2 and Figure E4 in the Online Repository).

Consistent with previous studies in African American adults[21] and Puerto Rican children,[23] African ancestry was nominally associated with lower pre- and post-bronchodilator FEV_1 and FVC in Mexican American, Puerto Rican and other Latino children with asthma, except for pre-bronchodilator FEV_1 in Mexican Americans that was not significant, but showed a trend in the same direction ($p=0.067$, Table 3). When all Latino groups in GALA II were combined, each 20% increase in African ancestry was significantly associated with lower pre-bronchodilator FEV_1 (−77±19 ml, meta-$p=5.8\times10^{-5}$) and FVC (−100±21 ml, meta-$p=2.7\times10^{-6}$), and lower post-bronchodilator measures of FEV_1 (−83±19 ml, meta-$p=1.1\times10^{-5}$) and FVC (−107±22 ml, meta-$p=1.0\times10^{-6}$) (Table 3; Figure E5). Native American ancestry was nominally associated with higher FVC measurements, but the effects were smaller than those observed for African ancestry (Table 3, Figure E6) and the results did not meet the Bonferroni significant threshold. No association was found between European ancestry and lung function (Figure E7). We then explored if Native American and African ancestry could account for the differences in lung function among Latino groups. Including genetic ancestry in the regression models to test for an association between ethnicity and lung function removed the association of ethnicity with FEV_1 and FVC (Table 2).

$FEF_{25–75}$ is clinically useful to identify children at risk for poor asthma outcomes, even in presence of normal FEV_1 values.[35] Therefore, we also evaluated the association of genetic ancestry with $FEF_{25–75}$ in Latino children with asthma. Each 20% increase in African ancestry was nominally associated with lower pre-bronchodilator and post-bronchodilator $FEF_{25–75}$ in all Latino groups in GALA II combined (−75±37 ml/s, meta-$p=0.041$ and meta-$p=0.045$, respectively) (see Table E5 in the Online Repository). However, these results were not significant after adjusting for multiple comparisons.

We next analyzed the association of genetic ancestry and lung function among controls, considering only the two measurements that were significant in asthma cases after Bonferroni correction (FEV_1 and FVC). Our results showed that African ancestry was also associated with lower lung function in controls at nominal significance (Table E6).

Discussion

We sought to determine whether genetic ancestry was associated with asthma susceptibility and lung function in three ethnic sub-groups of Latino children. A unique finding from this study is that Native American ancestry was associated with decreased odds of asthma among Mexican Americans and other Latinos from GALA II, and in Hispanic white individuals from the CHS study. In contrast, African ancestry was associated with increased odds of asthma in Puerto Ricans and other Latinos from GALA II. Furthermore, when we evaluated lung function among children with asthma, African ancestry was nominally associated with lower FEV_1 and FVC in all three Latino sub-groups in GALA II, even in Mexican individuals where the African admixture is more limited.

No prior study has tested nor identified an association between global Native American ancestry and asthma. Herein, we report the novel, replicated finding of a protective effect of Native American ancestry for asthma in Latinos. Although environmental factors can also be involved in asthma pathogenesis, the effect of Native American ancestry was independent from numerous environmental factors including SES and exposure to air pollution in GALA II,[26] suggesting the association of genetic ancestry with asthma is due to genetic causes. In support of this theory, a genome-wide association study (GWAS) in Mexicans identified a protective allele for asthma that was more common on Native American haplotypes.[8] In addition, the protective allele for the SNP rs907092 associated with asthma in a previous GWAS in GALA II [28] is more common Native American populations (40.0%) from North and South America than in populations from Africa (11.2%) according to The ALlele FREquency Database (ALFRED)[36] and in the Human Genome Diversity Project.[37] Interestingly, the SNP rs907092 is an expression quantitative trait loci (eQTL) for several genes in the region 17q21 (http://www.ebi.ac.uk/Tools/geuvadis-das), especially for *ORMDL3* ($p=9.1\times10^{-44}$). Also, another protective factor identified in that study,[28] local Native American ancestry at chromosome 6p21, has a higher frequency in Mexicans than in other Latinos and in Puerto Ricans (56.5%, 38.2%, and 21.1%, respectively). Therefore, the association of protective variants with Native American ancestry could in part explain the lower prevalence of asthma among Mexicans compared with other U.S. populations. Interestingly, a protective effect of Native American ancestry was not observed in Puerto Ricans, the ethnic group with the highest prevalence of asthma in the U.S. This may be attributed to the lower statistical power to identify a significant effect in Puerto Ricans (9% versus >99% in Mexicans and other Latinos) (Table E7). The limited statistical power in Puerto Ricans was due to the lower levels of Native American ancestry and the limited variability among individuals in this group:[38] Puerto Rican individuals had 11.3% of Native American ancestry (interquantile range [IQR]=3.3%) compared with 34.6% in other Latinos (IQR=41.5%), and 58.7% in Mexicans (IQR=23.7%). Another explanation, could be that the Native American ancestral component among Mexicans and Puerto Ricans is derived from different founder populations,[11,39–41] which may have varying frequencies of protective

alleles. Unfortunately, the Native population from Puerto Rico (Taíno) is extinct and cannot be used directly as a reference population, limiting our ability to make comparisons between the two Native American ancestral components. Another limitation of this study was the different definition of ethnicity between the different studies. However, using PCA we showed that individuals from CHS self-identified as Hispanic white were more similar to Mexicans from the GALA II and GALA I studies than to Puerto Ricans (Figure E3).

The association of African ancestry with higher odds of asthma in Puerto Ricans and other Latinos is consistent with results previously described in African American, African Caribbean, Colombian and Brazilian populations[18–20] and may partially explain the high prevalence of asthma in Puerto Ricans. African haplotypes may carry genetic factors that were historically protective against pathogens more common in Africa,[42] but are now a risk factor for asthma in urban westernized populations. For example, an allele that is protective for trypanosomiasis is also a risk factor for severe kidney disease, and is more common among individuals with African ancestry.[43] In fact, several genes associated with the diversity of helminth species also harbor risk alleles for asthma[44] and genetic variants protective for helminthic infection have been associated with risk for atopic wheeze and allergy.[45] We identified a risk effect of African ancestry on asthma susceptibility in Puerto Ricans and other Latinos in GALA II, but not in Mexicans from GALA II, GALA I, or CHS. This result is likely a function of reduced statistical power due to the low proportion and limited variability of African ancestry in Mexicans as compared with Puerto Ricans and other Latinos (Table E7). In all subgroups of Latinos, African ancestry was higher in cases than in controls, and no heterogeneity was found (p=0.134).

In a previous study, we identified a complex interaction between SES, genetic ancestry, and asthma susceptibility, with African ancestry increasing the odds of asthma only in individuals with high SES.[30] In addition, for other diseases it has been suggested that the degree of African ancestry, as measured by skin color, is associated with disease due to a correlation with lower SES alone.[46,47] However, in this study, the association of African ancestry with asthma susceptibility remained statistically significant following adjustment for various measures of SES. Our findings are consistent with the observation of similar asthma prevalence in Puerto Rico across various income categories[48] and studies where SES similarly failed to explain an association of African ancestry with asthma-related traits.[17,23] We also considered known early life exposures affecting asthma risk in the models, including NO_2 air pollution[26] and tobacco smoke.[49] While we cannot completely rule out the presence of confounding effects due to unmeasured environmental, early life exposures, cultural or behavioral factors,[50,51] our results suggest there is an important genetic component underlying the differences in asthma prevalence among Latino sub-groups. Additional studies including admixture mapping are necessary to identify the precise location of population-specific risk factors for asthma.[10]

The association of African ancestry with lower pulmonary function in Latino children with asthma is consistent with results found for African Americans[16,21] and Puerto Ricans.[23] Here we built upon and extended these findings to Mexicans and other Latinos. In addition, we described an association of Native American ancestry with higher lung function, as previously suggested.[9,24] This association was weaker than the one found for African

ancestry, even if we had enough statistical power to detect an association in the meta-analysis (Table E8), but is consistent with the identification of a protective effect for lung function decline and chronic obstructive pulmonary disease risk described in New Mexican Hispanics.[52] For the first time, we also demonstrated the proportions of African and Native American genetic ancestry can explain the higher lung function found in Mexicans compared with other Latinos and Puerto Ricans. Additionally, the difference in African ancestry proportions among Latino ethnic groups, argues against the use of spirometry reference equations derived from Mexicans for Puerto Rican individuals, as this may result in misclassification of lung function and disease severity.[21,53] Our results support the need for future studies to develop reference equations for Puerto Ricans. Our results are limited to the analysis of FEV_1, FVC, and $FEF_{25–75}$, but other lung function measurements such as FEV_1/FVC could be also informative of pulmonary obstruction and asthma severity.

In conclusion, we demonstrate that in addition to environmental and socioeconomic factor, genetic ancestry may partially explain differences in both asthma susceptibility and lung function across children from different Latino ethnic groups. Additional studies in diverse Latino populations are required to identify the genetic variation underlying these associations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

BMI	body mass index
CHS	Children's Health Study
CI	confidence interval
$FEF_{25–75}$	forced expiratory flow from 25% to 75% of forced vital capacity
FEV_1	forced expiratory volume in the first second
FVC	forced vital capacity
GALA I	Genetics of Asthma in Latino Americans
GALA II	Genes-environments & Admixture in Latino Americans
GWAS	genome-wide association study
IQR	interquantile range
OR	odds ratio
PCA	principal component analysis
SNP	single nucleotide polymorphism
SES	Socioeconomic Status
U.S.	United States

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Key Messages

- Among United States children, asthma prevalence is highest in Puerto Ricans and lowest in Mexicans. Although environmental factors are important explaining these differences, we demonstrated that Native American and African ancestry can also contribute to the variation in asthma prevalence among Latinos.
- Among Latinos, African ancestry is associated with lower lung function, measured by pre-bronchodilator and post-bronchodilator values of $FEV_1$and FVC

Capsule summary

In this study we demonstrated that disparities in asthma prevalence and lung function among Latinos can be partially explained by differences in the proportions of genetic ancestry, independently of early life exposures and socioeconomic status.

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Table 1

Summary of association of genetic ancestry with asthma susceptibility in GALA II (n=3,774), GALA I (n=321) and CHS (n=1,398), and in a meta-analysis across all studies.

Ancestry	Group	Mean ancestry cases	Mean ancestry controls	OR (95% CI)[a]	*p*-value
Native American	GALA II Mexicans	56.2	61.2	0.70 (0.60–0.82)	**9.6×10^{-6}**
	GALA II Other Latinos	32.7	36.5	0.73 (0.57–0.92)	**0.008**
	GALA II Puerto Ricans	11.4	11.1	2.18 (0.95–4.99)	0.377
	GALA I Mexicans	44.8	46.4	0.92 (0.54–1.57)	0.759
	CHS Latinos	35.9	42.1	0.70 (0.62–0.78)	**1.8×10^{-10}**
	Meta-analysis[b]	-	-	0.72 (0.66–0.78)	**1.5×10^{-15}**
African	GALA II Mexicans	4.2	3.8	2.18 (0.95–4.99)	0.066
	GALA II Other Latinos	17.6	16.4	1.62 (1.14–2.30)	**0.008**
	GALA II Puerto Ricans	21.9	20.4	1.29 (1.07–1.56)	**0.007**
	GALA I Mexicans	5.5	5.0	1.46 (0.12–18.28)	0.769
	CHS Latinos	5.0	4.7	1.13 (0.83–1.54)	0.425
	Meta-analysis[c]	-	-	1.40 (1.14–1.72)	**0.001**
European	GALA II Mexicans	39.6	35.1	1.44 (1.22–1.70)	**1.5×10^{-5}**
	GALA II Other Latinos	49.6	47.1	1.12 (0.85–1.47)	0.422
	GALA II Puerto Ricans	66.7	68.5	0.74 (0.61–0.89)	**0.002**
	GALA I Mexicans	49.7	48.6	1.07 (0.62–1.84)	0.804
	CHS Latinos	59.1	53.3	1.36 (1.22–1.51)	**6.1×10^{-9}**
	Meta-analysis[d]	-	-	1.13 (0.89–1.45)	0.316

[a] Odds of asthma for each ancestry compared with the other two ancestries and adjusting for age, sex, and recruitment region as covariates.

[b] A fixed effect meta-analysis was used as no heterogeneity across studies was detected (I^2=0%, p=0.088).

[c] A fixed effect meta-analysis was used as no heterogeneity across studies was detected (I^2=29%, p=0.166).

[d] A random effect meta-analysis was used as heterogeneity across studies was detected (I^2=88%, 0%, $p<10^{-4}$).

All the estimates of odds ratios and 95% confidence interval are referred to each increase of 20% in each ancestry.

p-values≤0.05 are in bold.

Table 2

Summary of association testing of ethnicity in GALA II asthma cases with pre-bronchodilator and post-bronchodilator measures of FEV1 and FVC. Puerto Rican and other Latino groups are compared with Mexicans (reference group).

		Unadjusted by African ancestry				Adjusted by African and Native American ancestry			
		Pre-bronchodilator		Post-bronchodilator		Pre-bronchodilator		Post-bronchodilator	
Measurement	**Group**	**Effect ± SE[a] (ml)**	***p*-value[a]**	**Effect ± SE[a] (ml)**	***p*-value[a]**	**Effect ± SE[a] (ml)**	***p*-value[a]**	**Effect ± SE[a] (ml)**	***p*-value[a]**
FEV_1	Other Latinos	−82±28	**0.009**	−62±28	**0.026**	−24±31	0.444	−3±31	0.923
	Puerto Ricans	−143±38	**1.5×10^{-4}**	−121±37	**0.001**	−75±44	0.091	−53±44	0.225
FVC	Other Latinos	−100±32	**0.002**	−91±33	**0.006**	−25±36	0.477	−10±4	0.788
	Puerto Ricans	−134±43	**0.002**	−127±44	**0.004**	−45±50	0.370	−30±52	0.566

[a] Adjusted for age, sex, height, height squared, use of controller medication and recruitment region as covariates.

p-values≤0.05 are in bold.

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Table 3

Results of association testing between genetic ancestry and lung function pre-bronchodilator and post-bronchodilator measures of FEV and FVC in children with asthma from GALA II.

			Pre-bronchodilator		Post-bronchodilator	
Measure	**Ancestry**	**Group**	**Beta ± SE (ml)**	***p*-value**	**Beta ± SE (ml)**	***p* -value**
FEV_1	Native American	Mexicans	26±20	0.184	26±20	0.189
		Other Latinos	23±25	0.370	18±25	0.472
		Puerto Ricans	112±63	0.074	118±62	0.059
		Meta-analysis	30±15	**0.047**	28±15	0.059
	African	Mexicans	−160±87	0.067	−218±86	**0.012**
		Other Latinos	−73±32	**0.024**	−91±32	**0.005**
		Puerto Ricans	−72±24	**0.003**	−68±24	**0.005**
		Meta-analysis	−77±19	$\mathbf{5.8\times10^{-5}}$	−83±19	$\mathbf{1.1\times10^{-5}}$
	European	Mexicans	−20±21	0.337	−16±21	0.433
		Other Latinos	24±27	0.379	41±26	0.124
		Puerto Ricans	57±25	**0.022**	53±25	**0.036**
		Meta-analysis	15±14	0.286	19±14	0.155
FVC	Native American	Mexicans	23±23	0.318	30±24	0.204
		Other Latinos	51±28	0.068	58±28	**0.041**
		Puerto Ricans	181±70	**0.010**	184±73	**0.012**
		Meta-analysis	43±17	**0.012**	50±18	**0.005**
	African	Mexicans	−242±102	**0.017**	−290±106	**0.006**
		Other Latinos	−114±36	**0.002**	−128±36	**0.001**
		Puerto Ricans	−81±27	**0.003**	−82±28	**0.004**
		Meta-analysis	−100±21	$\mathbf{2.7\times10^{-6}}$	−107±22	$\mathbf{1.0\times10^{-6}}$
	European	Mexicans	−12±24	0.628	−17±25	0.492
		Other Latinos	19±30	0.531	20±30	0.518
		Puerto Ricans	56±28	**0.047**	56±29	0.056
		Meta-analysis	18±16	0.263	16±16	0.337

Adjusted by age, sex, height, height squared, use of controller medication, and recruitment region as covariates. Effect estimates are expressed in ml and referred to each increase of 20% in each ancestry compared with the other two ancestries.

All meta-analyses were performed with a fixed effect model, as heterogeneity across samples was not detected ($p>0.05$).

p-values≤0.05 are in bold.