

African Ancestry is a Risk Factor for Asthma and High Total IgE Levels in African Admixed Populations

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ABSTRACT: Characterization of genetic admixture of populations in the Americas and the Caribbean is of interest for anthropological, epidemiological, and historical reasons. Asthma has a higher prevalence and is more severe in populations with a high African component. Association of African ancestry with asthma has been demonstrated. We estimated admixture proportions of samples from six trihybrid populations of African descent and determined the relationship between African ancestry and asthma and total serum IgE levels (tIgE). We genotyped 237 ancestry informative markers in asthmatics and nonasthmatic controls from Barbados (190/277), Jamaica (177/529), Brazil (40/220), Colombia (508/625), African Americans from New York (207/171), and African Americans from Baltimore/Washington, D.C. (625/757). We estimated individual ancestries and evaluated genetic stratification using Structure and principal component analysis. Association of African ancestry and asthma and tIgE was evaluated by regression analysis. Mean $\pm$ SD African ancestry ranged from 0.76 ± 0.10 among Barbadians to 0.33 ± 0.13 in Colombians. The European component varied from 0.14 ± 0.05 among Jamaicans and Barbadians to 0.26 ± 0.08 among Colombians. African ancestry was associated with risk for asthma in Colombians (odds ratio (OR) = 4.5, $P = 0.001$) Brazilians (OR = 136.5, $P = 0.003$), and African Americans of New York (OR: 4.7; $P = 0.040$). African ancestry was also associated with higher tIgE levels among Colombians ($\beta = 1.3$, $P = 0.04$), Barbadians ($\beta = 3.8$, $P = 0.03$), and Brazilians ($\beta = 1.6$, $P = 0.03$). Our findings indicate that African ancestry can account for, at least in part, the association between asthma and its associated trait, tIgE levels.

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KEY WORDS: African; asthma; ancestry

Introduction

Race and ethnicity are complex constructs incorporating social, cultural, and genetic factors. Populations that migrated from continental Africa as part of the African Diaspora were dispersed across the Americas, and their contemporary

ancestors have varying proportions of African admixture depending upon local demographic history and patterns of admixture, geographical location, and other factors [Via et al., 2011; Wang et al., 2008]. Determination of the ancestral origin and extent of the hybridization is of great anthropological, epidemiological, and historical interest and affords opportunities to study the evolutionary biology of the ancestral as well as the admixed populations.

Differences in African or other ancestry proportions between cases and controls is a confounding factor in genetic association studies of admixed populations because differences in admixture proportions among subgroups can erroneously suggest association with disease instead of ancestry at loci where allele frequencies differ between the ancestral populations (e.g., population stratification) [Cardon and Palmer, 2003; Spielman et al., 1993; Ziv and Burchard, 2003]. This situation is typically addressed by

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genotyping ancestry informative markers (AIMs) to estimate the individual ancestral proportions for major putative parental populations in admixed groups, and even though multiple approaches can be used, the underlying concept is to incorporate those values represented either as proportions of admixture or eigenvalues derived from principal component analysis (PCA) in the model used to evaluate genetic associations [McKeigue, 2007; Patterson et al., 2006; Pritchard and Rosenberg, 1999].

Alternatively, admixed populations provide a unique opportunity for interrogating the relationship between ancestry components and those biological traits and diseases that have different prevalences or degrees of severity among specific ethnic groups [Winkler et al., 2010]. It is well established that the prevalence, morbidity, and mortality of allergic airway diseases, such as asthma, is disproportionately high among individuals of African descent in the United States [Akinbami et al., 2005, 2011; El-Ekiaby et al., 2006; Gold et al., 1993; Lang et al., 2009; Lester et al., 2001; Moorman et al., 2007; Nelson et al., 1997; Sarpong et al., 1996; Schwartz et al., 1990], in African countries and countries with African admixture (i.e., Latin America) [Pearce et al., 2007]. The Global Strategy for Asthma Management and Prevention report suggests that African ancestry itself is a risk factor [GINA, 2008]. The usual source of airway inflammation in asthma is an immunoglobulin E (IgE)-mediated reaction initiated by exposure to environmental allergens, and asthma is closely associated with serum total IgE (tIgE) levels [Burrows et al., 1989; Marsh et al., 1974]. Higher serum tIgE levels have also been observed among African Americans with persistent asthma compared to whites and other ethnic groups [Grant et al., 2000; Grundbacher and Massie, 1985]. The differences are noticeable even early in life as described in a children cohort selected from a multiethnic society, where black newborns had significantly higher concentrations of cord blood serum tIgE compared with whites newborns [Haus et al., 1988]. It is unknown to what extent this is due to the environment versus genetic factors; however, a number of genetic variants identified as risk variants for asthma and associated traits have been shown to have significantly higher frequencies in individuals of African descent compared to other racial and ethnic groups [Barnes et al., 2007; Caggana et al., 1999; Green et al., 1998; Maxwell et al., 2005; Ness et al., 2004]. Also, a significant ancestry association peak on chromosome 6q14 (rs1361549) was associated with asthma exclusively in African American subjects with local European admixture [Torgerson et al.].

Previously, we observed an association between a well-established AIM of African ancestry, the Duffy antigen receptor for chemokines (DARC), and risk of asthma and high tIgE levels in independent African-admixed populations [Vergara et al., 2008]. Analyzing 44 AIMs, Choudhry and colleagues also established that African ancestry in general increased the risk for asthma among Puerto Ricans with higher socioeconomic status compared to those with lower socioeconomic status [Choudhry et al., 2006]. Kumar et al. demonstrated that African ancestry was inversely related to forced expiratory volume in 1 sec (FEV1) and forced vital capacity (FVC) in participants self-identified as African American in the Coro-

nary Artery Risk Development in Young Adults (CARDIA) study, the Health, Aging, and Body Composition (HABC) study, and the Cardiovascular Health Study (CHS) [Kumar et al., 2010], and in a recent publication, African ancestry was as predictor of early childhood wheezing in a prospective birth cohort of 1,034 children [Kumar et al., 2012]. Similarly, we estimated individual African ancestry using a panel of 52 AIMs in asthmatics and nonasthmatics from Cartagena (Colombia, South America), and determined that African ancestry was associated with a significant risk for asthma and high tIgE levels [Vergara et al., 2009]. Taking in account the relevance of replicating genetic associations [Chanock et al., 2007] and to expand our analyses and interrogate the strength of the association according to the degree of African ancestry in the population, we enlarged the AIMs panel to include 237 markers, and extended these studies to include additional, independent African Caribbean and African American populations from Colombia, Barbados, Jamaica, Brazil, and the United States. We estimated proportions of admixture of continental parental populations in those individuals and the relationship between African ancestry and asthma and serum tIgE levels.

Materials

Subjects

Barbadians

We included 467 Barbadian nonrelated individuals (190 cases and 277 nonasthmatic controls) from a study on the genetics of asthma as previously described [Barnes et al., 1996; Mathias et al., 2010] and in supplementary material and methods.

Jamaicans

A sample of 706 unrelated individuals (177 asthmatics, 529 nonasthmatic controls) was recruited from Kingston, St. Andrew, and St. Catherine, Jamaica as part of the Jamaican Adolescent Asthma Study as described in supplementary materials and methods and in references [Ashley et al., 1988; Tulloch-Reid et al., 2010]. All subjects provided informed written consent to participate as approved by the University of the West Indies, Mona campus.

Brazilians

Asthmatic ($N = 40$) and nonasthmatic ($N = 220$) nonrelated subjects were recruited in five rural communities (Buri, Camarao, Genipapo, Sempre Viva, and Cobo) in the district of Conde, Bahia, located in the North East Coast of Brazil as described in detail elsewhere [Grant et al., 2011; Vergara et al., 2008] and in Supporting Information material and methods. Written consent was obtained from adult individuals or parent or guardian of children as approved by the

Johns Hopkins Bayview Medical Center and Universidade de Federal de Bahia IRBs.

Colombians

A sample of 1,133 unrelated individuals (508 asthmatics and 625 nonasthmatic controls) were recruited from the Caribbean coastal city of Cartagena as described in detail elsewhere [Vergara et al., 2008, 2009] and in Supporting Information materials and methods. All subjects or their guardian/responsible adult gave written consent for their inclusion in the present study as approved by the Bioethics Committee of the School of Medicine of The University of Cartagena.

African Americans

Two samples of self-reported African Americans were included in this study. They were analyzed separately according to the recruiting site and place of residency of individuals. (1) A group of 1,382 individuals (625 asthma cases and 757 unrelated, unaffected controls) ascertained participating in *Genomic Research on Asthma in the African Diaspora* (GRAAD) recruited in the Baltimore-Washington D.C. metropolitan area and participants in the *Baltimore Asthma Severity Study* (BASS) residents of Baltimore City; (2) A second group comprising 378 individuals (207 asthmatic cases and 171 nonasthmatic controls) were recruited in New York and participated in *The Reducing Emergency Asthma Care in Harlem* (REACH) study. Details of these samples are described elsewhere [Ford et al., 2001; Mathias et al., 2007; Murray et al., 2010; Pesola et al., 2004] and in Supporting Information material and methods. The study protocols, recruitment procedures, and consent forms were approved by the Institutional Review Board of Columbia University, Johns Hopkins University, and Howard University.

tIgE Measurements

Sera were available in the Barbadian, Jamaican, Brazilian, Colombian, and African American samples from Baltimore-Washington, D.C. for measurements of tIgE as described previously [Vergara et al., 2008] and in supplementary Materials. For all datasets, tIgE values were log-transformed to reduce the skewness of the distribution. Measurements were not available for African Americans from New York and for participants of the BASS study.

Selection of AIMs and genotyping

We selected 237 AIMs distributed across 22 autosomes as presented in Supporting Information Table SI. The markers were a subset of 416 AIMs previously selected [Murray et al., 2010] from the 650Y panel based on a published list of AIMs [Cheng et al., 2009] showing large allelic frequency difference (δ) among the three putative parental populations

(European, African, and Asians) using HapMap Phase 2 reference populations (CEU, YRI, CHB), respectively.

Due to limitations in the availability of Native Americans DNA samples, for this analysis, we used Asians as a proxy for Native Americans because they are closely related [Bamshad et al., 2004]. Genotypes on HapMap subjects were downloaded from HapMart (<http://hapmart.hapmap.org/BioMart/martview>), an extension of the HapMap data resource. A marker was considered informative if 0.30 difference of the allelic frequencies existed between any of two parental groups. Blood samples were collected from all subjects and genomic DNA was extracted using standard protocols. Samples were genotyped according to the manufacturer's protocol at the Center for Inherited Disease Research on an Illumina BeadStation 500G Golden Gate genotyping platform using a custom panel (GS0011473-OPA). Genotyping plates were balanced by gender and asthma status and HapMap DNA samples and duplicates were included as genotyping controls.

Methods

Statistical Analysis

Comparisons of the demographic characteristics among asthmatics and nonasthmatics were performed by means of Student's *t*-test and χ^2 test as needed using STATA software (StataCorp. 2009. *Stata Statistical Software: Release 11*. College Station, TX: StataCorp LP.). Arlequin version 3.11 software [Excoffier et al., 2005] was used to calculate allele and genotype frequency of the AIMs, departure of genotype frequencies from Hardy-Weinberg equilibrium (HWE), linkage disequilibrium between each pair of markers (as an indicator of stratification) independently for each sample set and genetic differentiation among the analyzed populations using F_{ST} genetic distances [Reynolds et al., 1983; Slatkin, 1995]. Average population admixture and individual admixture estimates for each sample set were determined using a model-based clustering method by grouping data for the total sample in three ancestral populations ($K = 3$) to reflect the admixture history in the Caribbean and North and South America with the software Structure (version 2.3.3, <http://pritch.bsd.uchicago.edu/software>) and assessment of stratification was done by using PCA using the *smartpca* program from the software package *eigenstrat* [Patterson et al., 2006] including the three putative ancestral populations as reference. We investigated the relationship between disease status and African ancestry by logistic regression analysis using disease status as the dependent variable and individual ancestry as independent variable, while adjusting for potential confounders (age, sex). To determine associations of African ancestry with tIgE levels, a linear regression model was used incorporating age, sex, and disease status as covariates. When needed, *Glmer* and *lmer* packages in R were used to perform permutation analysis to confirm the association results with asthma and tIgE, respectively. For the association of African ancestry and tIgE levels, meta-analysis *P*-values were

computed using Stouffer's Z-score method [Stouffer et al., 1949].

Results

Subjects

Clinical and demographic characteristics of asthmatics and nonasthmatics in each sample are presented in Table I. Mean tIgE concentrations for each population were similar to those described previously [Grant et al., 2008; Vergara et al., 2009, 2008], wherein Brazilians showed higher tIgE levels than the other samples, most likely due to the high prevalence (83.5%) of extracellular parasitic disease in this population [de Jesus et al., 1993]. tIgE was significantly higher in asthmatics compared to nonasthmatics in all samples sets ($P \leq 0.001$) except Brazilians ($P = 0.64$). Results about allelic frequencies, HWE, genetic differentiation, and genetic structure are presented as supplementary material.

Admixture Estimates

Average ($\pm$ SD) population admixture estimate proportions are presented in Table II and individual admixture estimates are presented in Figure 1. The distribution of the African ancestry proportions are displayed as box plots in Supporting

Information Figure S1. Mean (SD) population African ancestry was highest in West Indians (Jamaicans, 0.76 ± 0.10 ; Barbadians, 0.76 ± 0.10) and African Americans from New York (0.70 ± 0.15) and Baltimore-Washington D.C. (0.69 ± 0.12) and lowest in the two South American samples (Brazilians, 0.45 ± 0.12 ; Colombians, 0.33 ± 0.13). The average European component ranged from a low of 0.14 ± 0.005 among Jamaicans and Barbadians to a high of 0.26 ± 0.08 among Colombians. The average Asian ancestry ranged from 0.08 ± 0.06 among Barbadians to 0.40 ± 0.13 among Colombians. There was a significant correlation between the first principal component and the estimates of individual African ancestry in each of the samples (Spearman's $\rho > 0.98$, $P < 0.0001$ for each pair of comparisons).

Association of African Ancestry and Asthma and tIgE

Table III summarizes results of regression analyses of African ancestry and asthma and tIgE. African ancestry was associated with a significant risk for asthma among several populations. The odds ratio (OR) for asthma is associated with a unit increase in African admixture proportion (from 0 to 1). It was significant for Colombians (OR: 4.5; 95% CI: 1.79–11.27; $P = 0.001$), Brazilians (OR: 136.5; 95% CI: 5.4–3405.6; $P = 0.003$), and African Americans of New York (OR: 4.7; 95% CI: 1.07–21.0; $P = 0.04$). In Brazilians, permutation

Table I. Descriptive characteristics of six African ancestry populations

Populations		N (%)	Male gender		Age		Total IgE [†]	
			N (%)	P value	Mean (SE)	P value	Geom. mean (95%CI)	P value
Barbadians	Asthmatics	190 (40)	67 (0.35)	0.02	40.1 (0.79)	0.0001	660.6 (389.0–1096.4)	0.001
	Controls	277 (59)	128 (0.46)		45.9 (0.71)		239.8 (186.2–301.9)	
Jamaicans	Asthmatics	177 (25)	80 (45)	0.51	18.8 (0.04)	0.7	213.8 (177.8–257.0)	0.001
	Controls	529 (75)	256 (48)		18.8 (0.03)		120.2 (107.1–134.8)	
Brazilians	Asthmatics	40 (15)	12 (30.0)	0.06	37.4 (3.30)	0.07	2526.5 (1769.7–3606.9)	0.6
	Controls	220 (85)	79 (35.9)		43.6 (1.23)		2294.1 (1957.6–2683.8)	
Colombians	Asthmatics	508 (45)	125 (24.6)	0.001	31.6 (0.73)	0.001	279.9 (247.1–318.0)	0.001
	Controls	625 (55)	309 (49.4)		36.7 (0.68)		424.6 (380.2–468.8)	
African American (New York [‡])	Asthmatics	207 (55)	129 (62.3)	0.001	40.3 (0.42)	0.005	NA	NA
	Controls	171 (45)	73 (42.6)		37.6 (0.87)		NA	
African Americans (Baltimore-Washington, D.C.) [‡]	Asthmatics	625 (45)	343 (45)	0.8	25.7 (0.62)	0.001	400.21 (342.9–467.0)	0.001
	Controls	757 (54)	323 (52)		33.2 (0.51)		187.4 (161.3–217.7)	

*NA: Not available; [†] Plus-minus values are means $\pm$ SE. Log-transformed total IgE concentrations measured in ng/ml. [‡] REACH, Reducing Emergency Asthma Care in Harlem.

[‡] BASS, Baltimore Asthma Severity Study; GRAAD, Genomic Research on Asthma in the African Diaspora.

Table II. African, European and Asian ancestry proportions for Barbadians, Jamaicans, Brazilians, Colombians and African Americans

Population	Ancestry proportions (Mean, SD)								
	African			European			Asian		
	Total	Asthmatics	Non asthmatic Controls	Total	Asthmatics	Non asthmatic Controls	Total	Asthmatics	Non asthmatic Controls
Barbadians	0.76 (0.10)	0.77 (0.11)	0.77 (0.10)	0.14 (0.05)	0.14 (0.04)	0.14 (0.05)	0.08 (0.07)	0.08 (0.08)	0.09 (0.06)
Jamaicans	0.76 (0.10)	0.76 (0.09)	0.77 (0.10)	0.14 (0.05)	0.14 (0.04)	0.14 (0.05)	0.09 (0.07)	0.10 (0.08)	0.09 (0.08)
Brazilians	0.45 (0.12)	0.52 (0.12)	0.45 (0.12)	0.19 (0.06)	0.18 (0.07)	0.19 (0.07)	0.34 (0.12)	0.29 (0.14)	0.35 (0.13)
Colombians	0.33 (0.13)	0.35 (0.13)	0.32 (0.14)	0.26 (0.08)	0.26 (0.08)	0.26 (0.08)	0.40 (0.13)	0.39 (0.13)	0.42 (0.13)
African Americans (New York)	0.70 (0.15)	0.71 (0.14)	0.68 (0.16)	0.15 (0.05)	0.15 (0.05)	0.15 (0.05)	0.14 (0.12)	0.14 (0.13)	0.16 (0.14)
African Americans (Baltimore-Washington, D.C.)	0.69 (0.12)	0.70 (0.14)	0.70 (0.12)	0.15 (0.05)	0.15 (0.06)	0.15 (0.05)	0.14 (0.12)	0.14 (0.11)	0.15 (0.13)

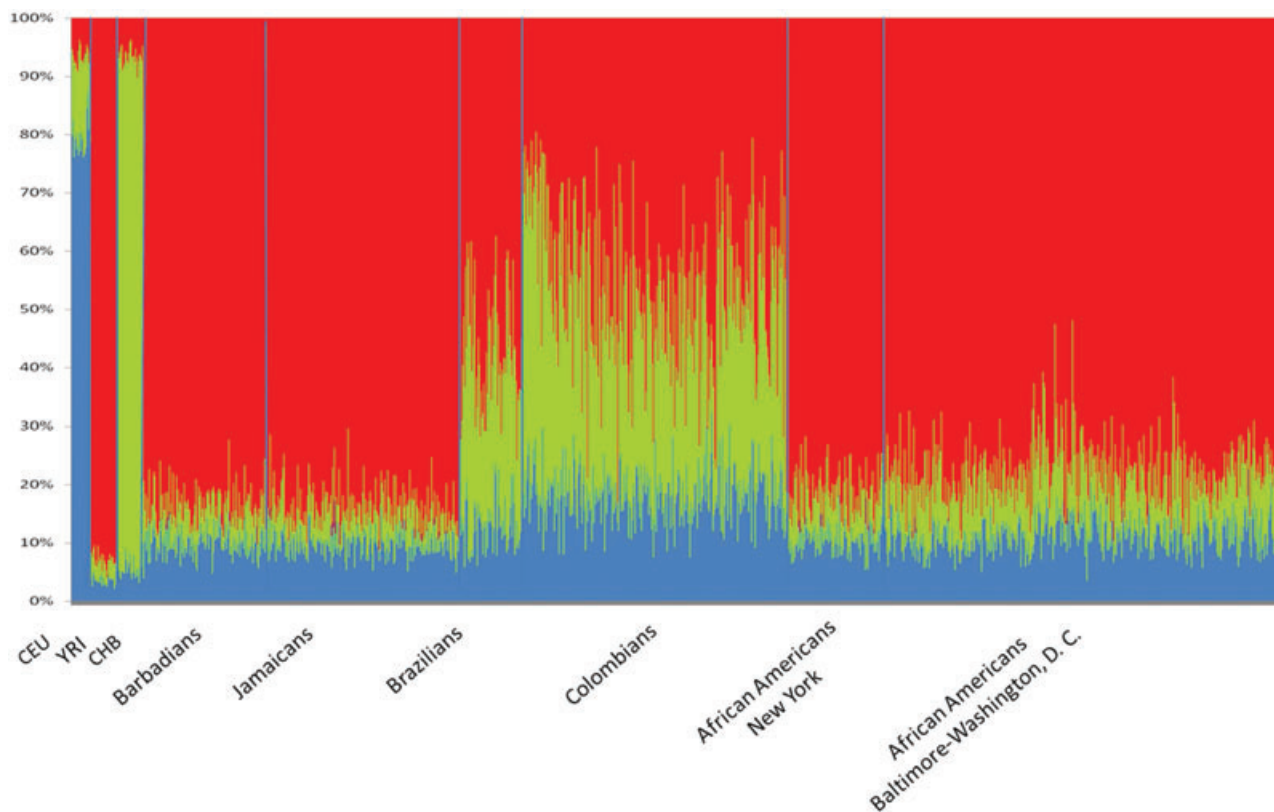


Figure 1. Individual admixture estimates by Structure for Barbadians ($N = 467$), Jamaicans ($N = 706$), Brazilians ($N = 260$), Colombians ($N = 1,133$), African Americans from New York ($N = 378$) and African Americans from Baltimore-Washington, D.C. ($N = 1,382$). Included are the putative parental populations available in HapMap (CEU, CHB, and YRI).

Table III. Results of regression analyses of African ancestry proportions and asthma and tIgE levels for Barbadians, Jamaicans, Brazilians, Colombians and two African American samples

Population	Asthma (OR, 95% CI, P value)*	Total serum IgE levels (β , 95% CI, P value)**
Barbadians	1.1 (0.16–6.9;0.9)	3.8 (1.1–13.1;0.03)
Jamaicans	0.8 (0.22–3.1;0.8)	1.0 (0.7–1.4;0.9)
Brazilians	136.5 (5.4–3406;0.003)	1.6 (1.1–2.6;0.03)
Colombians	4.5 (1.79–11.27;0.001)	1.3 (1.01–1.7;0.04)
African Americans (New York)	4.7 (1.07–21.04;0.04)	NA [#]
African Americans (Baltimore-Washington, D.C.)	1.1 (0.50–2.81;0.7)	0.99 (0.6–1.7;0.9)

*Adjusted by age and sex; **Adjusted by age, sex and asthma status. #NA = Not available. The odds ratio (OR) for asthma is associated with a unit increase in African admixture proportion (from 0 to 1).

analysis confirmed the association ($P = 0.001$). Principal component plots for each sample of each population are shown in Supporting Information Figure S2. The plotted individuals are discriminated by affection status. For the Jamaican and the two African American populations, cases and controls clustered together and there was no significant difference in the distribution of the first principal component among asthma cases and nonasthmatic controls for each sample. For Colombians and Brazilians and African Americans from New

York, a significant difference was found when comparing the distribution of the first principal component among cases and nonasthmatic controls ($P < 0.001$).

Of the five samples with tIgE data available, African ancestry was associated with tIgE levels in Colombians (β : 1.3; 95% CI: 1.01–1.7; $P = 0.04$), Barbadians (β : 3.8; 95% CI: 1.1–13.1; $P = 0.030$), and Brazilians (β : 1.6; 95% CI: 1.1–2.6; $P = 0.03$; Permutation $P = 0.05$). No relationship between African ancestry and asthma or tIgE was detected among the Jamaicans or African American of Baltimore-Washington, D.C. No relationship between ancestry and asthma or tIgE was detected among the Jamaicans or African American of Baltimore-Washington, D.C. No associations were observed between European ancestry and asthma and/or tIgE in any of the datasets. Supporting Information Figure S4 graphically shows the effect (β) and 95% CI for the association of African ancestry and tIgE levels in each one of the analyzed population and the P -value calculated for all populations. The P -value of the meta-analysis of the five analyzed populations was statistically significant ($P = 0.019$).

Discussion

In this study, we determined the admixture proportion of six samples from populations of African descent

representing geographical regions across Continental America and two islands in the Caribbean, for which the African Diaspora figured prominently in the demographic history of these populations. We also investigated the association of African ancestry and asthma and tIgE levels including a sample of considerable size for each population and a comprehensive panel of AIMs distributed across the genome.

We included only self-reported unrelated individuals in each of the analyzed populations to minimize the potential effect of relatedness in calculations of allelic frequencies of the AIMs and consequently in the ancestry estimates and association analysis. Also, African Americans from Baltimore-Washington DC, African Americans from New York and Barbadians included in this study were previously analyzed using a Genome Wide Association Study (GWAS) panel of and all individuals identified as related by IBD analysis were removed from the dataset prior to this analysis [Mathias et al., 2010]. Additional cryptic relatedness could be elucidated by a larger panel of markers in the other populations but we do not think it would have a significant effect on our association analysis. We observed a wide range of average proportions of parental populations across the samples and a significant association of African ancestry and asthma and serum tIgE levels. To date, measured by number of populations included, sample size per populations, and number of AIMs, this is one of the largest studies to analyze ancestry proportions and the relationship with asthma and tIgE in populations of the Americas and the Caribbean.

Although each one of the analyzed populations has a unique history, they share certain characteristics regarding to the dynamics of the admixture process. Historical records indicate that there were generally three parental populations, West Africans, Europeans, and Native Americans. The process of admixture extended across Latin America and the Caribbean during the 15th through 19th centuries, including the arrival of Europeans (predominantly Spanish, Portuguese, and British) and the extinction of Native Americans converging with the arrival and expansion of African slaves, largely from West Africa during the 16th and 19th centuries. Nevertheless, the analyzed populations underwent diverse patterns of admixture given the location of settlement of the parental populations approximately 500 years ago [Curtin, 1969; Salzano, 2002; Sanchez-Albornoz, 1974; Thomas 1997].

In several previous genetic studies evaluating samples from the same contemporary countries of continental America included in the current study, ancestry estimates vary by region, as displayed in Supporting Information Table SIII. Several factors contributed to make up the current genetic pool including admixture, genetic drift, migration, and recent genetic flow [Winkler et al., 2010]. Asian ancestry estimates, which are a surrogate for Native American ancestry are the lowest of the three parental components in Barbadians, Jamaicans, and African Americans. Asian ancestry estimates obtained with this set of AIMs showed a large variation, and, we conclude these estimates may well be erroneous rather than indicative of admixture in contrast to estimates for the other two parental populations. It is well known that the Na-

tive American population was decimated and exterminated along the whole continent either by disease or labor [De las Casas, 1985; Simon, 1953; Williams, 1984]. For instance, there was a rapid annihilation of the Arawak population following colonization of the Spaniards from 1494 to 1655 in Jamaica; a similar history was described for the Caribs and Arawaks in Barbados [Rouse, 1992] and for the Caribs and Taironas in Cartagena [Meisel and Aguilera, 1997].

We found a predominant proportion of African ancestry and a low proportion of European ancestry in the populations of the Caribbean Islands. According to the records, the number of African slaves brought to work in the sugar plantation in Barbados was around 900,000 [Pepin, 2005] and outnumbered European settlers by a proportion of 20:1 [Simms et al., 2010]. Europeans were also decimated by disease and the predominant population that finally contributed to the contemporary genetic pool was of African origin [Benn-Torres et al., 2008; Knight, 1997]. A history that is very similar to that described in the island of Jamaica [Benn-Torres et al., 2008]. In continental America, a highly diverse genetic makeup has been noted previously including territories of Colombia and Brazil (Supporting Information Table SIII). Local history, diversity of the geography, as well as social and economic factors may have played a crucial role in the dynamic of admixture after the first admixture event. African admixture is especially pronounced in the coastal states, which underwent a social history similar to the rest of the Caribbean, whereby African slaves were imported as agricultural labor. In Colombia, a higher African ancestry has been detected in those places that were port of entry for slaves (Cartagena, Choco) or located in the route of transportation of slaves through the inner country and those regions close to the original sugar cane plantations [Rojas et al., 2010]. A high variation in admixture proportions has also been observed in different regions of Brazil among and within studies, however there has been a pattern observed indicating higher European ancestry in southern Brazil compared to the north as well as isolated populations of predominant African descent that do not follow this pattern [Pena et al., 2009; Santos et al., 2010]. If we compare our results to previous ones in the included populations (Supporting Information Table SIII), the estimates obtained are slightly different to those described before which can be attributable to the markers chosen, the samples analyzed, and the statistical methods used in the studies. Nevertheless, we consider that the admixture estimates obtained using this panel of markers is accurate. The current estimates are very consistent with those obtained with a significant higher number of markers in the same individuals of Barbados and African Americans of Baltimore-Washington DC [Murray et al., 2010] and the estimates obtained for the Colombian population were different compared with those obtained in the same individuals using a panel of 52 AIMs [Vergara et al., 2009]. These patterns of variation in ancestry across countries seem to be a common feature across the Americas even in small islands as Puerto Rico [Via et al., 2011]. This has large repercussion for genetic association studies in Latin American populations, given the high probability of population stratification, even in samples

from a single country or a geographic region, and highlights the relevance of correcting by using ancestry estimates in any genetic association study in these populations.

We observed a pattern correlating the geographic proximity of the samples and the genetic differentiation values observed with two independent statistical approaches (F_{ST} values and PCAs, Supporting Information Table SII and Figure S2). Brazilians and Colombians tended to cluster together (F_{ST} : 0.02, $P = 0.001$), close to the CEU samples and further apart from the West African cluster. In contrast, African Americans, Barbadians, and Jamaicans clustered very closely to each other and to the YRI samples, which is consistent with the low level of genetic differentiation detected by the F_{ST} statistic in those groups.

In this study, we found that African ancestry conferred a significant risk for asthma and higher levels of serum tIgE in comparison with non-African ancestries. The associations were not due to potential confounders as gender and age. We previously observed the association of African ancestry with asthma and tIgE levels in family-based association analyses investigating the relationship between a unique polymorphism in the gene encoding the DARC, a well-known marker of African ancestry as conferring risk for asthma and tIgE in a similar group of populations [Vergara et al., 2008]. In subsequent analyses, we investigated a Colombian case/control database and genotyped a set of 52 AIMs with similar results (OR for asthma associated with African admixture was 2.97 (95% CI: 1.08–8.08) and for tIgE 1.9 (95% CI: 1.17–3.12) [Vergara et al., 2009]. In this case, we replicated our findings with the same direction of the effect for asthma and tIgE in Brazilians and in Colombians (this time using a larger dataset and a higher number of AIMs), for asthma in African Americans from New York, and for tIgE in Barbadians. When comparing our results to those described in other admixed populations, we found that outcomes varied according to the populations and phenotype analyzed, design of the studies, and covariates included. Our results are highly consistent with those recently published for African Americans of the REACH cohort, where it was determined an OR of 1.16 (95% CI: 1.06–1.28; $P = 0.002$) for the risk of asthma per 10% increase of African ancestry after correcting by age, gender, and study site [Flores et al., 2012]. Similarly, in a Puerto Rican population, asthma risk increased with African ancestry among individuals with higher socioeconomic status [Choudhry et al., 2006] and European ancestry conferred risk for asthma in those from lower socioeconomic status [Choudhry et al., 2006]. In Mexican Americans, higher European ancestry was significantly associated with more severe asthma as measured by both FEV1 and by a clinical assessment of severity among Mexican Americans [Salari et al., 2005]. There are some differences between Salari et al.'s study and the current study, however, that may explain the discrepancy in the results, including the analyzed phenotypes (FEV1 vs. asthma/IgE) and the ancestries analyzed (European compared to Native American vs. African compared to European/Asian). Moreover, among Mexican Americans, the African component is low and not evaluable. In terms of IgE, even though the phenotype is not identical, our result are

similar to those described by Kumar et al., who determined that African ancestry was associated with increased odds of peanut and milk specific IgE levels of ≥ 5 kUA/L in children from an urban multiethnic birth cohort [Kumar et al., 2011].

Individual genetic ancestries as determined by AIMs have been also described as an important determinant of variation of multiple traits and/or susceptibility to other diseases. Among African American, Hispanic American, and European American children, a greater African admixture proportion has been associated with lower fat mass, lower total abdominal adipose tissue, lower intraabdominal adipose tissue, lower subcutaneous abdominal adipose tissue, and higher bone mineral content, after adjusting for socioeconomic status, sex, age, height, race/ethnicity, and pubertal status [Cardel et al., 2010]. Percentage of African ancestry was also inversely associated with function measurements (FEV1, FVC) in three independent cohorts of African Americans across a wide range of ages [Kumar et al., 2010]. In our study, we observed no associations between African ancestry and asthma in the African American group from Baltimore-Washington, D.C., Barbadians, and Jamaicans. The lack of association with asthma observed these populations could be attributed to the low variance of the African ancestry proportions in these populations (Supporting Information Figure S1) and low proportions of European and Asian ancestries, which in turn underpowered the comparisons. Among African Americans from the Baltimore-Washington D.C. metropolitan area, the sample size had power of only 0.25 to detect an OR of 4, given the European ancestry proportions and the case/control relation in those populations [Gauderman, 2006]. Power was even lower for Jamaicans and Barbadians, where a considerably larger sample size ($N = 2,757$ for Barbados and $N = 2,182$ for Jamaica) would be required to adequately evaluate the effect. Environmental factors, effect of socioeconomic status, different strategies for recruiting that potentially determine light differences in the asthma phenotype can also account for the lack of association in those groups.

The replication of our results in several populations with the same direction of the effect provide evidence that genetic factors contained in the African genetic component of hybrid populations contribute to ethnic disparities for asthma, and that studying populations of West African descent should help to identify additional genetic risk factors associated with asthma susceptibility. For example, Choudhry et al. performed admixture mapping for asthma including Puerto Rican individuals with moderate-to-severe asthma and nonasthmatic controls and identified chromosomal regions 5q23.3 and 13q13.3 as potential regions harboring genes for asthma in this population [Choudhry et al., 2008]. Differences in association in candidate genes for asthma according to ancestry have also been identified, indicating that specific and maybe different genetic risk factors account for asthma susceptibility in African descent populations compared with European descent populations [Barnes et al., 2007; Baye et al.]. We are aware of several caveats in our study design, one of which is the use of Asian populations as representative of Native American populations. Another

limitation is the lack of adjustment by socioeconomic status, a potentially critical confounder. Even though the Colombian samples used in this study were selected using the same approach as a previous report, in which the association of African ancestry and asthma remained after correcting for socioeconomic status [Vergara et al., 2009], we did not have access to the same level of socioeconomic status in the other populations in this study, and were therefore unable to evaluate the effect of this potential confounder. In summary, among populations of African descent distributed in different areas of the Americas and the Caribbean, African ancestry confers a significant risk for asthma and high tIgE levels. Population structure is an important confounding factor that can be efficiently corrected with this comprehensive set of markers in any future association studies. These populations are an excellent tool to examine loci associated with asthma and tIgE by admixture mapping.

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African Ancestry Is a Risk Factor for Asthma and High Total IgE Levels in African Admixed Populations

Supplementary Materials

Subjects.

Barbadians. We included founders of families ascertained through asthmatic probands from Barbados. They were recruited through referrals at local polyclinics or the Accident and Emergency Department at the Queen Elizabeth Hospital as previously described [Barnes, et al. 1996a; Barnes, et al. 1996b; Mathias, et al. 2010; Zambelli-Weiner, et al. 2005]. Asthma was defined as both a reported history of asthma and documented history of physician-diagnosed asthma (past or current), plus a history of wheezing without an upper respiratory infection (URI) for two out of four hallmark symptoms (wheezing with a URI, cough without a URI, shortness of breath, and tightness in the chest). All subjects gave verbal and written consent as approved by the Johns Hopkins Institutional Review Board (IRB) and the Barbados Ministry of Health.

Jamaicans. This group is a birth cohort of young African Caribbean adults previously characterized for asthma. Participants' mothers were initially recruited into the Jamaica Perinatal Mortality Survey of 1986, which included all children born in Jamaica in September and October of 1986 [Ashley, et al. 1988; Tulloch-Reid, et al. 2010]. Children were contacted at ages 11 and 16 as part of a child development study, and at age 18 for a cardiovascular study. Asthmatic subjects and controls were recruited from an existing birth cohort of young adults. Asthma was defined according to the ISAAC questionnaire [Asher, et al. 1995] and a history of physician-diagnosed asthma (past/current). Willing participants were asked to give blood samples for storage and future genotyping and for serum for measuring total IgE levels according to the approved protocol.

Brazilians. An ISAAC questionnaire was administered to obtain data on asthma symptoms [Mallol, et al. 2000; Sole, et al. 1998]. Basic demographic information and data on environment exposure was also

collected. Willing participants were asked to provide blood samples for storage and future genotyping and for serum for measuring total IgE levels. Children under the age of 6 were excluded.

Colombians. Asthma was defined using GINA criteria [GINA 2005] by using a standardized questionnaire previously tested [Caraballo, et al. 1992; Dennis, et al. 2004] in patients with a history of physician-diagnosed asthma as previously described [Vergara, et al. 2009; Vergara, et al. 2008].

African Americans: Individuals included in BASS and REACH samples were recruited as part of two separate but complementary programs. The *Reducing Emergency Asthma Care in Harlem* (REACH) study consists of adult residents of Central Harlem or West Harlem who visited the Harlem Hospital Center ED for an asthma exacerbation, and spoke English. Non-asthmatic controls were selected from the same ED. A structured, comprehensive asthma questionnaire was administered and a blood sample was collected for genetic studies. Selected individuals underwent venipuncture, skin testing and spirometry at a subsequent visit [Ford, et al. 2001]. Participants in the *Baltimore Asthma Severity Study* (BASS) were recruited through community-based clinics and non-clinical, community-based venues throughout Baltimore City. Phenotypic characterization of both asthmatic individuals and non-asthmatic controls includes a standardized questionnaire (including family history), allergy skin testing and serum collection for serum total IgE. Individuals with asthma responded to additional questions about determinants of asthma severity, and underwent spirometry with bronchodilators. Eligibility included self-identified resident of Baltimore City; 18 to 40 years of age; a nonsmoker; and a blood sample collection. Cases had to have a physician diagnosis of asthma. Exclusion criteria included chronic lung diseases other than asthma; a significant medical illness (e.g., HIV); current smoking or a smoking history of >15 pack-years; pregnancy; and immunotherapy. Controls reported no history or physician diagnosis of asthma or allergies and no bronchial hyper-responsiveness [Ford, et al. 2001]. Individuals included in the GRAAD group were cases and non-asthmatic controls from the Baltimore-Washington, D.C. metropolitan area who self-reported as African American ethnicity. This consortium represent eight separate, NIH-funded studies of asthma in pediatric and adult African American populations, plus one study on healthy African

Americans as previously described [Mathias, et al. 2010]. Informed consent was obtained from each study participant, and the study protocol was approved by the institutional review board at either the Johns Hopkins University or Howard University. For the purpose of this study, individuals from BASS and GRAAD were analyzed as a unique African American sample from Baltimore-Washington, D.C. area and those subjects recruited as part of REACH were analyzed as a separate cohort as representing the New York area.

Total IgE measurements: Total IgE (tIgE) levels in African Americans from GRAAD and Barbadians were measured through use of microplate tIgE assays performed by a central laboratory (Access Immunoassay System, Sanofi Pasteur Diagnostics) and the Chemiluminometric immunoassay (Magic Lite Total IgE Extended Range; ALK, Copenhagen, Denmark/CIBA-Corning, Medfield, MA) as previously described [Barnes, et al. 1996a; CSGA 1997]. In Colombians, tIgE was determined using a commercial enzyme-linked immunosorbent assay (ELISA) kit (RIDASCREEN ® Total IgE; R-Biopharm, Darmstadt, Germany) as described elsewhere [Martinez, et al. 2007]. In Brazilians, tIgE levels were measured using chemiluminescence (ADVIA Centaur Bayer Corporation, Salvador, Brazil) and a ratio of intensity of response was obtained using a confirmed non-allergic reference sample [Grant, et al. 2006]. In Jamaicans, tIgE was determined using ImmunoCAP250 (ThermoFisher Scientific, USA). Values are expressed as ng/ml.

Methods:

Statistical analysis.

Linkage disequilibrium between AIMs. Linkage disequilibrium was calculated as the difference between the observed haplotype frequencies, inferred by means of an expectation maximization method [Excoffier and Slatkin 1995] and the expected frequencies, which are a function of the observed allele frequencies for a pair of markers and follows a χ^2 distribution.

Correlation between individual admixture estimates and eigenvalues. Individual admixture estimates with the software STRUCTURE (version 2.3.3, <http://pritch.bsd.uchicago.edu/software>) and principal component analysis (PCA) was performed with the application *smartpca* from the software package *eigenstrat* [Patterson, et al. 2006]; in both analyses three putative ancestral populations were included as reference. Correlation between principal component coefficients and individual admixture estimates were calculated as Spearman ρ coefficients. P values ≤ 0.05 were considered statistically significant.

Validation of the panel of AIMs: In order to validate the panel of AIMs, estimates of ancestry using the current panel were compared to estimates of ancestry using a previous panel of 416 AIMs in the population of Barbados (N=265) and African Americans from the Baltimore-Washington, DC metropolitan area (N=649), and 52 AIMs in the sample from Colombia (N= 630).

Results

Allelic frequencies and HWE: Table I in supplementary material summarizes the chromosomal locations of the 237 AIMs according to HapMap Public Release #27 (2009-02-06), which combines genotype and frequency data for the three phases of the HapMap project (I+II: rel #24 and III: release #2) in NCBI build 36 (dbSNP b126). Allelic frequencies in the three putative ancestral populations and corresponding δ values between parental populations are also summarized. The average δ for all markers was 0.71 African/European populations, 0.48 for African/Asian populations, and 0.3 for European/Asian populations. Tests of HWE were performed for each marker independently for each dataset. Significant departures at $\alpha = 0.05$ after Bonferroni correction (P -corrected = 0.0002) were detected in one marker among Brazilians (0.04%), 18 among Colombians (7.5%), one marker among Jamaicans (0.04%), and 25 among African Americans from New York (10%) and these were eliminated from further analyses.

Genetic differentiation: Table II in supplementary material summarizes the population pair-wise F_{ST} values for each pair of analyzed populations. Each population significantly differentiates from the others and the parental populations ($P < 0.01$). The F_{ST} values were low but statistically significantly ($P < 0.001$)

when pairing the West African (YRI) population with African Americans from New York ($F_{ST}= 0.05$), African Americans from Baltimore-Washington, D.C. ($F_{ST}= 0.04$), Jamaicans ($F_{ST}=0.02$) and Barbados ($F_{ST}= 0.02$) but higher when the YRI population was compared to populations with a higher European contribution such as Brazilians ($F_{ST}= 0.22$) and Colombians ($F_{ST}=0.28$). The opposite was observed when comparing the European parental population with the admixed populations. The higher values of differentiation were observed between CEU and African Americans from New York ($F_{ST}= 0.47$), African Americans from Baltimore-Washington ($F_{ST}= 0.45$) and Barbadians ($F_{ST}= 0.56$) and the lowest were found between CEU and Brazilians and Colombians ($F_{ST}=0.25$ and $F_{ST}=0.15$, respectively). Within the admixed populations, the lowest F_{ST} values were observed between African Americans from New York and African Americans from Baltimore-Washington, D.C. ($F_{ST}=0.0014$) and the highest between Colombians and Jamaicans or Barbadians ($F_{ST}=0.21$). F_{ST} calculations between CEU vs. YRI are higher from those previously described [Price, et al. 2008] probably due to a standard error around the estimate given the set of markers included in this study. PCA yielded two significant axes of variation. The first PC captured the dominant African vs. non-African admixture; the variation explained by the first PC varied from 22.3% in Brazilians to 45.1% in Jamaicans. The second PC seems to capture a gradient between Asian and European populations; the variation captured by this PC varied from 1.5% in Brazilians to 2.3% in Jamaicans. Figure 2 in supplementary material shows the plot of the top two principal components in the total number of individuals in each sample and the HapMap Phase 2 reference populations. Results of the PCA is consistent with the observed F_{ST} values; Colombians and Brazilians clustered together indicating a higher genetic proximity within them and in a equivalent distance from the YRI and CEU populations compatible with a similar proportion of European and African ancestries. Jamaicans, Barbadians and African Americans clustered together and closer to the YRI population than to the CEU population. Brazilians and Colombians located further away from Jamaicans, Barbadians and African Americans.

Genetic structure: Individual admixture estimates are presented in Figure 1. Results indicated the presence of substructure in each sample from different populations. The STRUCTURE program consistently assigned individuals to three groups with a higher probability than it did to a single group or two groups, *e.g.*, $\ln P(D) = -1308899$ for $K = 1$, whereas $\ln P(D) = -1128979$ for $K = 2$ and $\ln P(D) = -1124853$ for $K = 3$. The presence of genetic structure was also observed using a second test on each sample of every population: pairwise haplotypes were created with all markers typed to assess whether the admixture process had created a detectable disequilibrium between them. In each population, more than 60% of the unlinked markers were significantly associated ($P < 0.05$), significantly higher than the 5% of significant associations expected by chance. The first two principal components of the PCA (as presented in supplementary Figure 2) strongly support the notion that the ancestral populations contributing to the diversity of the African descent populations included in this study correspond to Asian, European, and African ancestry. The six analyzed populations showed different profiles of ancestry, as exemplified by their locations in the covariance matrix of each population's first two PCs (Supplementary Figure 2). When analyzed by asthma status (Supplementary Figure 3), Jamaicans and African Americans of Baltimore-Washington area cases and controls formed a unique cluster. For Colombians and Brazilians and African Americans from New York, a significant difference was found when comparing the distribution of the first principal component among cases and non-asthmatic controls in each sample ($P < 0.001$).

Validation of the panel of AIMs: Figure 5 in Supplementary material shows the accuracy of the ancestry estimates obtained with the AIMs panel for Barbadians, African Americans and Colombians. The individual ancestry estimates based on the current AIMs panel were compared to the estimates based on 416 AIMs for Barbadians and a subgroup of the African Americans of Baltimore-Washington DC area as well as the estimates based in the 52 panel described previously in a sample from Colombia. There was a strong concordance for the samples from Barbadians and African Americans and a lower concordance for the panel in Colombians.

Supplementary Tables:

Table I. Rs numbers, chromosome position, reference allele, allele frequencies of the AIMs in parental and admixed populations and δ value for each pair of parental populations.

Rs Number	Chr	Position	Allele	YRI	CEU	CHB	YRI/ CHB	YRI/ CEU	CEU/ CHB
rs4908343	chr1	27804285	G	0.98	0.20	0.35	0.63	0.79	0.16
rs359955	chr1	32907361	A	0.79	0.20	0.23	0.56	0.58	0.03
rs710232	chr1	41975741	A	0.20	0.99	0.74	0.54	0.78	0.24
rs596985	chr1	64049623	A	0.24	0.99	0.80	0.57	0.76	0.19
rs290829	chr1	97224265	A	0.92	0.16	0.44	0.48	0.76	0.28
rs2003154	chr1	110551800	A	0.21	0.87	0.95	0.74	0.66	0.08
rs1923949	chr1	190814333	A	0.02	0.79	0.57	0.55	0.77	0.22
rs3006246	chr1	198298703	C	0.14	0.72	1.00	0.86	0.58	0.28
rs1340117	chr1	206897234	A	0.30	0.97	0.76	0.46	0.67	0.21
rs2666839	chr1	212882847	G	0.25	0.93	0.80	0.55	0.68	0.13
rs2008602	chr1	218098941	G	0.96	0.30	0.71	0.25	0.66	0.41
rs1110379	chr1	223167277	G	0.05	0.89	0.72	0.68	0.84	0.17
rs493950	chr1	226673588	A	0.14	0.93	0.63	0.49	0.79	0.30
rs6586395	chr1	232715442	A	0.15	0.92	0.99	0.84	0.77	0.07
rs7525142	chr1	238809528	G	0.02	0.81	0.52	0.51	0.80	0.29
rs11897977	chr2	1363732	A	0.24	0.92	0.70	0.45	0.68	0.22

rs9309717	chr2	3474085	A	0.04	0.73	0.49	0.44	0.68	0.24
rs921599	chr2	20654606	G	0.88	0.16	0.21	0.67	0.71	0.04
rs13025681	chr2	26602008	T	0.94	0.21	0.32	0.62	0.73	0.11
rs2631941	chr2	29834790	G	0.94	0.12	0.21	0.73	0.82	0.09
rs4643526	chr2	61038155	G	0.08	0.83	0.97	0.89	0.75	0.14
rs4267542	chr2	69084554	A	0.16	0.94	0.45	0.30	0.78	0.49
rs1444543	chr2	80527125	C	0.04	0.79	0.21	0.17	0.75	0.58
rs1025104	chr2	86204175	A	0.94	0.14	0.29	0.65	0.80	0.15
rs10171578	chr2	104632896	A	0.19	0.94	0.51	0.32	0.75	0.44
rs260714	chr2	108928927	C	0.16	0.90	0.02	0.14	0.74	0.88
rs6750983	chr2	122995726	G	0.91	0.08	0.21	0.70	0.83	0.13
rs1979038	chr2	148927368	A	0.82	0.10	0.03	0.79	0.73	0.07
rs901303	chr2	163124693	G	0.10	0.95	0.48	0.38	0.85	0.47
rs12466967	chr2	174052326	A	0.87	0.10	0.41	0.46	0.78	0.31
rs6710083	chr2	192480837	G	0.13	0.94	0.98	0.84	0.81	0.04
rs920249	chr2	201020574	A	0.81	0.11	0.29	0.51	0.70	0.19
rs1473636	chr2	212590435	T	0.79	0.10	0.04	0.76	0.70	0.06
rs3755152	chr2	216530442	A	0.70	0.08	0.30	0.40	0.62	0.22
rs1868929	chr2	231891835	C	0.32	0.95	0.41	0.09	0.63	0.54
rs155412	chr3	1329463	A	0.06	0.89	0.86	0.80	0.83	0.03
rs7622872	chr3	61277754	A	0.73	0.09	0.01	0.72	0.64	
rs2623382	chr3	100550148	C	0.03	0.88	0.58	0.55	0.85	0.30
rs9288952	chr3	113667715	G	0.89	0.04	0.23	0.66	0.86	0.20
rs1909808	chr3	123808157	G	0.24	0.91	0.82	0.59	0.68	0.09
rs1027858	chr3	131785876	C	0.84	0.14	0.49	0.34	0.70	0.36

rs641320	chr3	139830647	G	0.17	0.94	0.99	0.82	0.78	0.05
rs3796259	chr3	142461611	C	0.14	0.76	0.56	0.42	0.62	0.20
rs13099104	chr3	174130861	T	0.89	0.33	0.35	0.55	0.57	0.02
rs7653308	chr3	193645745	C	0.24	0.89	0.88	0.64	0.64	0.00
rs6782303	chr3	199130633	T	0.07	0.78	0.78	0.71	0.71	0.00
rs4552452	chr4	10033421	G	0.82	0.19	0.35	0.47	0.63	0.17
rs2872795	chr4	16939479	T	0.91	0.24	0.51	0.40	0.67	0.27
rs7689639	chr4	25184635	G	N/A	0.85	0.51	0.51	0.85	0.34
rs4623048	chr4	41528244	C	0.01	0.79	0.96	0.95	0.78	0.18
rs7663168	chr4	67020209	T	0.13	0.79	0.98	0.85	0.66	0.19
rs4694666	chr4	75286706	C	0.89	0.07	0.18	0.71	0.82	0.11
rs2178603	chr4	85309773	A	0.02	0.81	0.56	0.54	0.79	0.25
rs6814827	chr4	91559691	T	0.06	0.86	0.65	0.59	0.80	0.21
rs7657799	chr4	105594872	T	0.18	0.96	0.80	0.62	0.78	0.15
rs1525760	chr4	117354829	C	0.93	0.11	0.10	0.82	0.81	0.01
rs6534487	chr4	126671424	C	0.22	0.90	0.56	0.34	0.68	0.34
rs10016932	chr4	131396357	A	0.06	0.79	0.59	0.53	0.73	0.20
rs2407548	chr4	152069974	T	0.88	0.06	0.28	0.60	0.81	0.22
rs2877558	chr4	171979791	G	0.09	0.89	0.73	0.64	0.80	0.16
rs13107001	chr4	176636581	G	0.88	0.06	0.10	0.79	0.82	0.03
rs4861584	chr4	185102115	T	0.33	0.96	0.48	0.15	0.64	0.48
rs378257	chr5	2571738	C	0.04	0.82	0.66	0.63	0.78	0.16
rs12109816	chr5	19786897	C	0.87	0.13	0.29	0.58	0.74	0.16
rs7727623	chr5	28248480	C	0.89	0.21	0.60	0.29	0.68	0.39
rs7735863	chr5	31522297	A	0.73	0.09	0.49	0.23	0.64	0.41

rs930072	chr5	36701828	C	0.96	0.10	0.72	0.24	0.86	0.62
rs6881896	chr5	55508312	C	0.09	0.90	0.54	0.45	0.81	0.36
rs7712760	chr5	64075218	A	0.11	0.67	0.52	0.41	0.56	0.15
rs874973	chr5	72773651	A	0.13	0.93	0.51	0.38	0.80	0.42
rs10474347	chr5	90602254	A	0.90	0.16	0.43	0.47	0.75	0.27
rs294152	chr5	104486852	C	0.79	0.06	0.13	0.66	0.73	0.07
rs4631225	chr5	108840383	A	0.10	0.86	0.58	0.48	0.76	0.27
rs1382342	chr5	115589027	C	0.91	0.22	0.31	0.60	0.69	0.09
rs261532	chr5	138929546	G	0.01	0.72	0.90	0.89	0.71	0.18
rs4513684	chr5	147632278	A	0.15	0.99	0.66	0.51	0.84	0.33
rs7729084	chr5	174314186	A	0.26	0.94	0.95	0.69	0.68	0.00
rs6597398	chr6	925237	A	0.17	0.91	0.89	0.72	0.74	0.01
rs4276549	chr6	8825098	G	0.75	0.06	0.10	0.66	0.69	0.03
rs7770341	chr6	16276393	A	0.29	0.94	0.70	0.41	0.65	0.25
rs11966463	chr6	22111874	A	0.33	0.95	0.71	0.38	0.62	0.24
rs195429	chr6	37462413	C	0.27	0.91	0.85	0.58	0.64	0.06
rs619572	chr6	42425545	A	0.22	0.92	0.58	0.36	0.69	0.34
rs7766458	chr6	54248087	A	0.16	0.88	0.73	0.57	0.72	0.15
rs11963862	chr6	91829068	T	0.11	0.90	0.61	0.50	0.79	0.30
rs197870	chr6	95613585	G	0.24	0.94	0.64	0.41	0.71	0.30
rs9386887	chr6	110754613	T	0.17	0.88	0.69	0.52	0.71	0.20
rs362949	chr6	146694047	T	0.21	0.96	0.86	0.65	0.75	0.10
rs11155751	chr6	151137072	G	0.13	0.80	0.51	0.38	0.67	0.29
rs2803358	chr6	158127916	G	0.06	0.76	0.10	0.04	0.70	0.66
rs745285	chr6	170380250	A	0.09	0.81	0.54	0.45	0.72	0.27

rs187985	chr7	23392757	A	0.09	0.85	0.80	0.71	0.76	0.05
rs2107550	chr7	30884888	G	0.10	0.83	0.61	0.51	0.73	0.22
rs37268	chr7	41305505	T	0.04	0.82	0.57	0.54	0.79	0.25
rs260368	chr7	46429867	A	0.20	0.84	0.58	0.39	0.64	0.25
rs10270964	chr7	50856620	C	0.77	0.06	0.18	0.60	0.72	0.12
rs844684	chr7	71132933	A	0.22	0.91	0.65	0.43	0.70	0.26
rs2110871	chr7	77918484	A	0.95	0.30	0.48	0.47	0.65	0.18
rs7807771	chr7	84986899	A	0.39	0.93	0.88	0.48	0.54	0.05
rs10488004	chr7	90596172	A	0.85	0.24	0.52	0.34	0.62	0.28
rs4728417	chr7	136790470	C	0.81	0.06	0.53	0.28	0.74	0.47
rs6464211	chr7	151504786	C	0.17	0.87	0.71	0.54	0.70	0.16
rs11136757	chr8	4447323	T	0.81	0.16	0.12	0.69	0.64	0.04
rs1523643	chr8	16833606	G	0.93	0.05	0.46	0.48	0.88	0.41
rs926105	chr8	24776396	G	0.91	0.26	0.26	0.65	0.65	0.00
rs4732619	chr8	27933188	A	0.90	0.23	0.30	0.61	0.67	0.07
rs4237080	chr8	34900051	A	0.14	0.89	0.44	0.29	0.75	0.46
rs2923419	chr8	42585573	G	0.93	0.08	0.15	0.78	0.85	0.07
rs13439780	chr8	56506740	C	0.16	0.97	0.87	0.71	0.81	0.10
rs1866694	chr8	62335222	C	0.08	0.86	0.16	0.08	0.78	0.71
rs346617	chr8	73406911	T	0.74	0.16	0.06	0.68	0.58	0.10
rs1375781	chr8	84135108	C	0.81	0.19	0.19	0.63	0.62	0.01
rs2978133	chr8	95164339	T	0.17	0.73	0.50	0.33	0.56	0.23
rs17840659	chr8	111488705	A	0.12	0.93	0.90	0.79	0.81	0.02
rs12547950	chr8	123685278	G	0.23	0.93	0.91	0.68	0.70	0.02
rs780321	chr8	127152877	T	0.89	0.21	0.06	0.83	0.69	0.14

rs4367565	chr8	131607137	A	0.09	0.80	0.66	0.57	0.71	0.15
rs7831261	chr8	135416154	C	0.05	0.77	0.69	0.64	0.73	0.09
rs10809101	chr9	1048914	A	0.12	0.75	0.54	0.42	0.64	0.22
rs324498	chr9	9049545	G	0.76	0.12	0.19	0.57	0.63	0.06
rs1331675	chr9	13167389	A	0.96	0.34	0.44	0.52	0.62	0.10
rs4879592	chr9	32687114	C	0.19	0.84	0.63	0.44	0.66	0.22
rs1887455	chr9	37478725	C	0.19	0.64	0.61	0.43	0.46	0.03
rs1331473	chr9	70404546	T	0.81	0.18	0.30	0.52	0.63	0.12
rs1935338	chr9	73228986	T	0.95	0.23	0.51	0.44	0.72	0.28
rs6477733	chr9	98664884	T	0.26	0.98	0.64	0.38	0.72	0.34
rs2230808	chr9	106602625	T	0.92	0.20	0.43	0.49	0.72	0.23
rs3780528	chr9	112707098	T	0.24	0.84	0.96	0.72	0.60	0.12
rs4144636	chr9	118802528	T	0.91	0.16	0.24	0.67	0.75	0.08
rs590086	chr9	132333480	C	0.82	0.10	N/A		0.73	
rs5029224	chr9	139843620	A	0.24	0.99	1.00	0.76	0.75	0.01
rs1326207	chr10	15206911	A	0.05	0.72	0.83	0.78	0.67	0.11
rs11101394	chr10	49475222	T	0.68	0.00	0.13	0.55	0.67	0.13
rs10761587	chr10	52319199	T	0.89	0.13	0.20	0.69	0.75	0.06
rs224136	chr10	64140681	C	0.14	0.86	0.73	0.60	0.72	0.13
rs7908565	chr10	76421441	A	0.15	0.85	0.57	0.42	0.70	0.28
rs10736103	chr10	98086005	T	0.74	0.02	N/A		0.72	
rs9418990	chr10	135187956	C	0.90	0.21	0.49	0.41	0.69	0.28
rs2403595	chr11	12341885	T	0.89	0.09	0.06	0.83	0.80	0.03
rs4378393	chr11	21560867	G	0.15	0.92	0.78	0.63	0.77	0.14
rs1561937	chr11	25541756	G	0.91	0.06	0.04	0.87	0.85	0.02

rs549272	chr11	30419686	A	0.17	0.86	0.51	0.33	0.69	0.36
rs10768140	chr11	35467483	T	0.90	0.28	0.66	0.24	0.62	0.38
rs1030774	chr11	38454177	G	0.87	0.06	0.35	0.53	0.81	0.28
rs10792837	chr11	85583363	G	0.88	0.14	0.32	0.56	0.74	0.18
rs1452673	chr11	96757835	G	0.93	0.24	0.02	0.92	0.69	0.23
rs7103514	chr11	117325771	A	0.24	0.93	0.72	0.48	0.69	0.21
rs10744614	chr12	3425163	A	0.85	0.15	0.22	0.63	0.70	0.07
rs3782711	chr12	6053442	T	0.17	0.89	0.80	0.64	0.72	0.08
rs1861482	chr12	11724925	A	0.90	0.15	0.17	0.73	0.75	0.02
rs7975017	chr12	26320060	T	0.87	0.20	0.19	0.69	0.68	0.01
rs4931655	chr12	32949329	G	0.84	0.06	0.20	0.64	0.78	0.14
rs7306523	chr12	51680231	A	0.98	0.12	0.73	0.25	0.85	0.60
rs899653	chr12	56170068	G	0.85	0.16	0.39	0.46	0.70	0.23
rs460406	chr12	71298182	A	0.94	0.20	0.56	0.38	0.74	0.36
rs10859541	chr12	92534318	A	0.25	0.95	0.63	0.38	0.70	0.32
rs4767252	chr12	113672107	A	0.93	0.31	0.71	0.22	0.62	0.40
rs2615667	chr12	124569401	C	0.20	0.84	0.29	0.09	0.65	0.56
rs1885894	chr13	21545183	A	0.93	0.21	0.38	0.55	0.72	0.17
rs943724	chr13	26172270	G	0.89	0.22	0.45	0.44	0.67	0.23
rs1329667	chr13	33389838	A	0.91	0.21	0.51	0.40	0.70	0.30
rs1572018	chr13	40613282	T	0.99	0.15	0.60	0.39	0.84	0.46
rs3751380	chr13	48049420	G	0.20	0.97	0.89	0.69	0.77	0.08
rs7321057	chr13	50580015	C	0.20	0.92	0.68	0.48	0.72	0.24
rs1622710	chr13	59004926	T	0.84	0.07	0.17	0.67	0.78	0.11
rs7333151	chr13	72517230	A	0.20	0.93	0.97	0.77	0.73	0.05

rs9788393	chr13	93042338	G	0.91	0.23	0.76	0.15	0.68	0.53
rs9582807	chr13	103578174	T	0.14	0.93	0.77	0.63	0.79	0.16
rs9522149	chr13	110625168	T	0.97	0.24	0.99	0.02	0.73	0.75
rs6572731	chr14	22307675	C	0.81	0.16	0.24	0.58	0.66	0.08
rs3784191	chr14	31993041	C	0.11	0.87	0.64	0.53	0.76	0.23
rs1956424	chr14	36601653	G	0.26	0.96	0.79	0.53	0.70	0.17
rs987644	chr14	78313798	A	0.98	0.13	0.36	0.63	0.85	0.23
rs11159698	chr14	84835008	A	0.09	0.81	0.57	0.47	0.72	0.25
rs3825663	chr14	89499502	A	0.13	0.96	0.96	0.84	0.83	0.01
rs2369049	chr14	95241604	A	0.16	0.87	0.94	0.78	0.71	0.07
rs1003229	chr14	97241370	G	0.93	0.19	0.08	0.84	0.74	0.11
rs1131877	chr14	102411802	T	0.05	0.78	0.62	0.57	0.73	0.16
rs10142224	chr14	105079690	C	0.26	0.98	0.87	0.62	0.73	0.11
rs6576431	chr15	21333294	A	0.70	N/A	N/A			
rs7173247	chr15	31246185	C	0.18	0.86	0.71	0.53	0.68	0.15
rs1873813	chr15	51082540	C	0.11	0.80	0.43	0.32	0.69	0.37
rs974828	chr15	58642847	C	0.05	0.93	0.84	0.79	0.88	0.09
rs8033972	chr15	62312033	G	0.00	0.75	0.87	0.86	0.75	0.12
rs4777126	chr15	67294514	T	0.87	0.12	0.25	0.62	0.76	0.14
rs6495489	chr15	78409622	A	0.05	0.68	0.35	0.30	0.63	0.34
rs8040248	chr15	82519409	C	0.21	0.87	0.40	0.19	0.66	0.47
rs4965117	chr15	96293254	T	0.05	0.77	0.62	0.57	0.72	0.15
rs4965814	chr15	99631440	C	0.93	0.15	0.46	0.46	0.77	0.31
rs6500552	chr16	3699394	T	0.07	0.72	0.59	0.52	0.65	0.13
rs7204918	chr16	12823080	T	0.05	0.88	0.67	0.62	0.82	0.20

rs13335375	chr16	15926090	C	0.13	0.92	0.96	0.83	0.79	0.04
rs1503949	chr16	22866185	T	0.10	0.90	0.88	0.78	0.80	0.02
rs8046826	chr16	46730882	G	0.89	0.23	0.12	0.78	0.66	0.11
rs3843712	chr16	65491654	T	0.16	0.88	0.74	0.57	0.71	0.14
rs9928718	chr16	73634239	G	0.83	0.10	0.26	0.58	0.74	0.16
rs4280248	chr16	84619550	T	0.06	0.83	0.38	0.32	0.77	0.46
rs7208188	chr17	113034	C	0.11	0.88	0.71	0.60	0.78	0.17
rs212498	chr17	29755162	G	0.93	0.31	0.11	0.83	0.62	0.20
rs2593595	chr17	38309771	A	0.01	0.77	0.85	0.83	0.76	0.07
rs903104	chr17	68536297	A	0.75	0.14	0.21	0.54	0.61	0.07
rs8074370	chr17	74468926	T	0.83	0.12	0.74	0.09	0.70	0.61
rs439890	chr18	3710081	C	0.18	0.93	0.84	0.66	0.75	0.09
rs629699	chr18	8825869	G	0.86	0.24	0.16	0.70	0.63	0.07
rs2155771	chr18	24818125	A	0.13	0.90	0.82	0.69	0.77	0.08
rs647853	chr18	38442742	T	0.03	0.77	0.17	0.14	0.74	0.60
rs11082588	chr18	43244969	C	0.89	0.20	0.29	0.60	0.69	0.09
rs4377248	chr18	60013901	A	0.21	0.95	0.90	0.69	0.75	0.05
rs4891724	chr18	64961189	G	0.87	0.10	0.38	0.50	0.77	0.28
rs634392	chr18	68367025	A	0.80	0.05	0.66	0.14	0.75	0.61
rs590218	chr18	72198871	G	0.81	0.11	0.17	0.64	0.70	0.06
rs1865028	chr19	5966066	T	0.24	0.99	0.93	0.69	0.75	0.06
rs8113531	chr19	9104893	A	0.34	1.00	0.96	0.62	0.66	0.04
rs2052474	chr19	11517995	T	0.19	0.94	0.85	0.66	0.75	0.09
rs6511061	chr19	19915823	G	0.16	0.93	0.80	0.64	0.77	0.13
rs867815	chr19	34225922	A	0.08	0.83	0.44	0.36	0.74	0.39

rs10553	chr19	37779881	A	0.28	0.99	0.56	0.28	0.71	0.43
rs2231738	chr19	45141888	T	0.16	0.89	0.70	0.54	0.74	0.20
rs3745099	chr19	57593717	G	0.93	0.12	0.38	0.55	0.81	0.26
rs890869	chr19	60324855	C	0.14	0.87	0.51	0.36	0.73	0.36
rs16990309	chr20	4784440	C	0.19	0.88	0.85	0.66	0.69	0.03
rs2294306	chr20	7817025	A	0.18	0.97	0.61	0.43	0.79	0.36
rs2876410	chr20	15502753	A	0.98	0.24	0.39	0.59	0.75	0.16
rs6101991	chr20	38515722	A	0.13	0.91	0.85	0.71	0.77	0.06
rs914828	chr20	45050724	T	0.83	0.06	0.51	0.32	0.77	0.44
rs4811429	chr20	51458409	C	0.22	0.93	0.80	0.58	0.70	0.12
rs1028546	chr20	53171407	C	0.92	0.13	0.13	0.79	0.78	0.00
rs16984321	chr20	58809363	C	0.19	0.92	0.95	0.76	0.73	0.03
rs310644	chr20	61629948	T	0.06	0.89	0.96	0.90	0.83	0.07
rs380417	chr21	26194030	T	0.84	0.18	0.51	0.33	0.66	0.33
rs2070398	chr21	29800235	T	0.93	0.18	0.39	0.54	0.75	0.22
rs2834670	chr21	35202246	A	0.03	0.82	0.64	0.62	0.79	0.17
rs1209914	chr21	39074242	G	0.95	0.29	0.52	0.42	0.66	0.24
rs9618000	chr22	16233714	A	0.26	0.85	0.71	0.45	0.59	0.14
rs737796	chr22	20768050	G	0.15	0.87	0.69	0.54	0.73	0.19
rs11703808	chr22	30354980	A	0.93	0.39	0.77	0.17	0.55	0.38
rs4823209	chr22	42992777	T	0.22	0.89	0.55	0.34	0.68	0.34

Table II. Pairwise F_{ST} values for each pair of comparison of the admixed and parental populations. All comparison were statistically significant ($P < 0.0001$)

	Brazil	Colombia	Jamaica	Barbados	Afr. Americans New York	Afr. Americans Balto.-Wash.	CEU	YRI	CHB
Brazil	-								
Colombia	0.02	-							
Jamaica	0.15	0.21	-						
Barbados	0.15	0.21	0.0043	-					
African Americans New York	0.09	0.15	0.01	0.01	-				
African Americans Baltimore-Washington, D.C.	0.09	0.16	0.01	0.01	0.0014	-			
CEU	0.25	0.15	0.54	0.56	0.47	0.45	-		
YRI	0.22	0.28	0.02	0.02	0.05	0.04	0.69	-	
CHB	0.11	0.06	0.39	0.40	0.31	0.31	0.18	0.52	-

Table III. Admixture estimates obtained in previous analyses in the populations included in the current study.

Population	N (geographic region)	Ancestry estimates, mean (%)			
		African	European	Native American	Reference
Barbadians	95	89.6	10.2	0.2	[Benn-Torres, et al. 2008]
	272	77.4	15.9	6.7	[Murray, et al. 2010]
	467	76	14	8	Current study
Jamaicans	54	84.4	12.4	3.2	[Benn-Torres, et al. 2008]
	102	NA	6.8	NA	[Parra, et al. 1998]
	119	78.3	16.0	5.7	[Simms, et al. 2010]
	706	76	14	9	Current study
Brazilians	40 (North)	18.2	71.1	10.7	[Lins, et al. 2010]
	40 (Northeast)	13.6	77.4	8.9	[Lins, et al. 2010]
	40 (South East)	14.1	79.9	6.1	[Lins, et al. 2010]
	40 (Center West)	18.7	69.5	11.8	[Lins, et al. 2010]
	40 (South)	7.0	87.7	5.2	[Lins, et al. 2010]
	146 (North)	24	34	42.0	[Resque, et al. 2010]

	235 (North East)	36	37	27	[Resque, et al. 2010]
	226 (South East)	35	38	27	[Resque, et al. 2010]
	138 (South)	20	46	34	[Resque, et al. 2010]
	49 (North -East)	14.2	71.1	14.7	[Pena, et al. 2009]
	196(North-East Amazon)	11.7	61.4	26.9	[Santos, et al. 2010]
	81 (Southern brazil)	1.0	95	4	[Santos, et al. 2010]
	103 (Amazon region)	80.7	9.3	10	[Santos, et al. 2010]
	260	45	19	34	Current study
Colombians	64 (Antioquia)	88.5	0	11.5	[Gomez-Perez, et al. 2010]
	34 (Antioquia)	19.3	60.0	20.7	[Gomez-Perez, et al. 2010]
	19 (Antioquia)	6	52	39	[Galanter, et al. 2012]
	183 (North coast)	43.8	23.3	32.9	[Rojas, et al. 2010]
	733 (North Coast)	38.3	43.0	18.6	[Vergara, et al. 2009]
	22 (Southern)	2	17	80	[Galanter, et al. 2012]
	19 (Central)	2	9	86	[Galanter, et al. 2012]
	36 (Southern)	2	16	83	[Galanter, et al. 2012]
	1133 (North Coast)	33	26	40	Current study

African Americans	96	NA	15.5	NA	[Parra, et al. 1998]
	906	72.3	19.7	8%	[Murray, et al. 2010]
	246	86.2	NA	NA	[Lao, et al. 2010]
	329 (REACH)	81.5	NA	NA	[Flores, et al. 2012]
	467 (BASS)	78.5	NA	NA	[Flores, et al. 2012]
	321 (CHIRAH)	79.7	NA	NA	[Flores, et al. 2012]
	378 (New York)	70	15	14	Current study
	1382 (Baltimore Washington DC)	69	15	14	Current study

Supplementary Figures:

Figure 1. Boxplots of the distribution of the African ancestry proportions on the total sample for Barbadians, Jamaicans, Brazilians, Colombians, African Americans from New York and Baltimore-Washington, D.C. Each box represents the median and interquartile range.

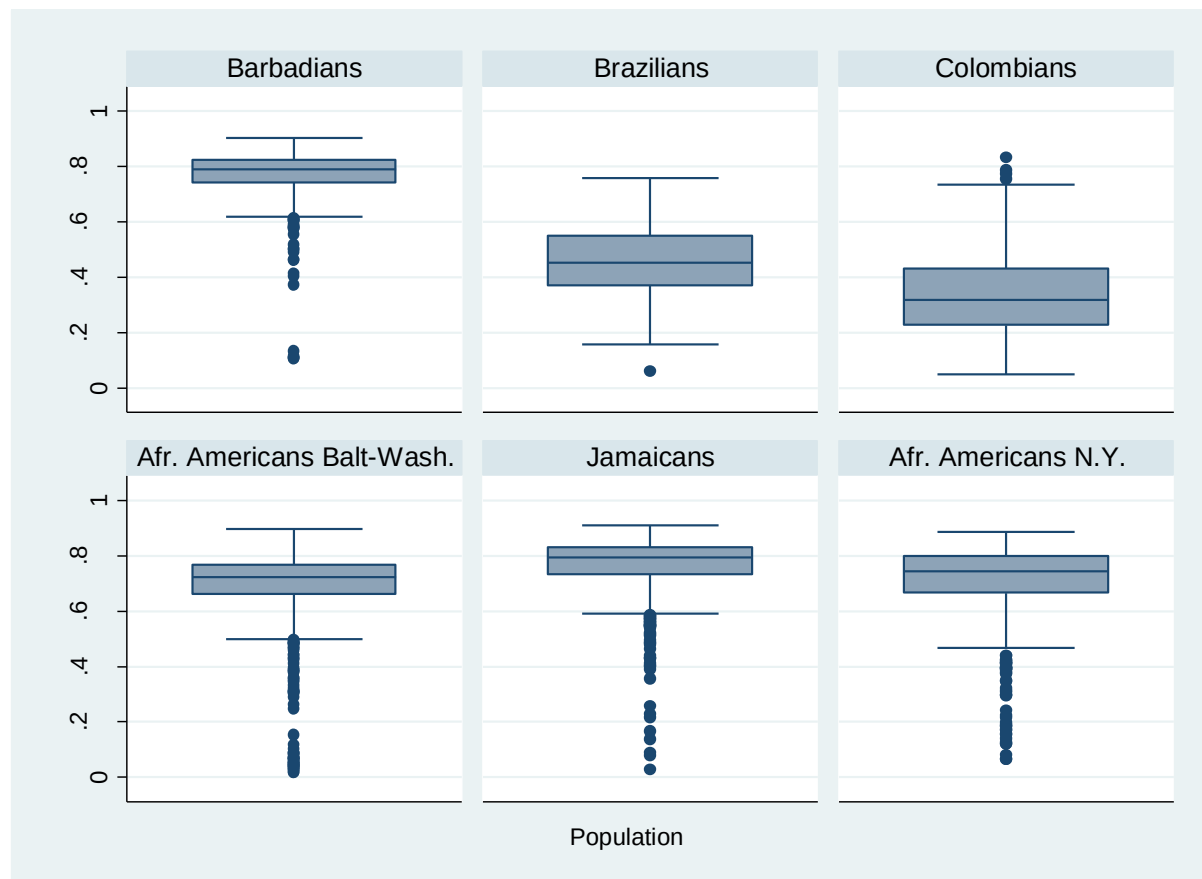


Figure 2. Plots of the top two principal components (PC1 and PC2) on the total sample from Barbados, Jamaica, Brazil, Colombia, African Americans from New York and African Americans from Baltimore-Washington, D.C. Included are the putative parental populations available in HapMap (CEU, CHB and YRI).

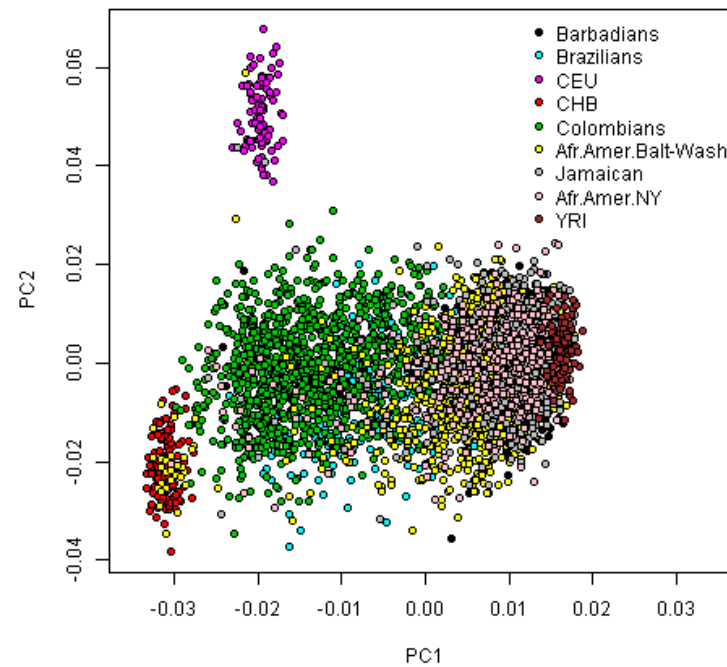


Figure 3. Plots of the first principal components (PC1, PC2) from analysis on (A) Barbadians (N=467), (B) Jamaicans (N=706), (C) Brazilians (N=260), (D) Colombians (N=1133), (E) African Americans from New York (N=378) and (F) African Americans from Baltimore-Washington, D. C. (N = 1382). Individuals are color plotted by asthma status (Cases/Controls). Included are the putative parental populations available in HapMap (CEU, CHB and YRI). Individuals were color plotted according to asthma status in each sample.

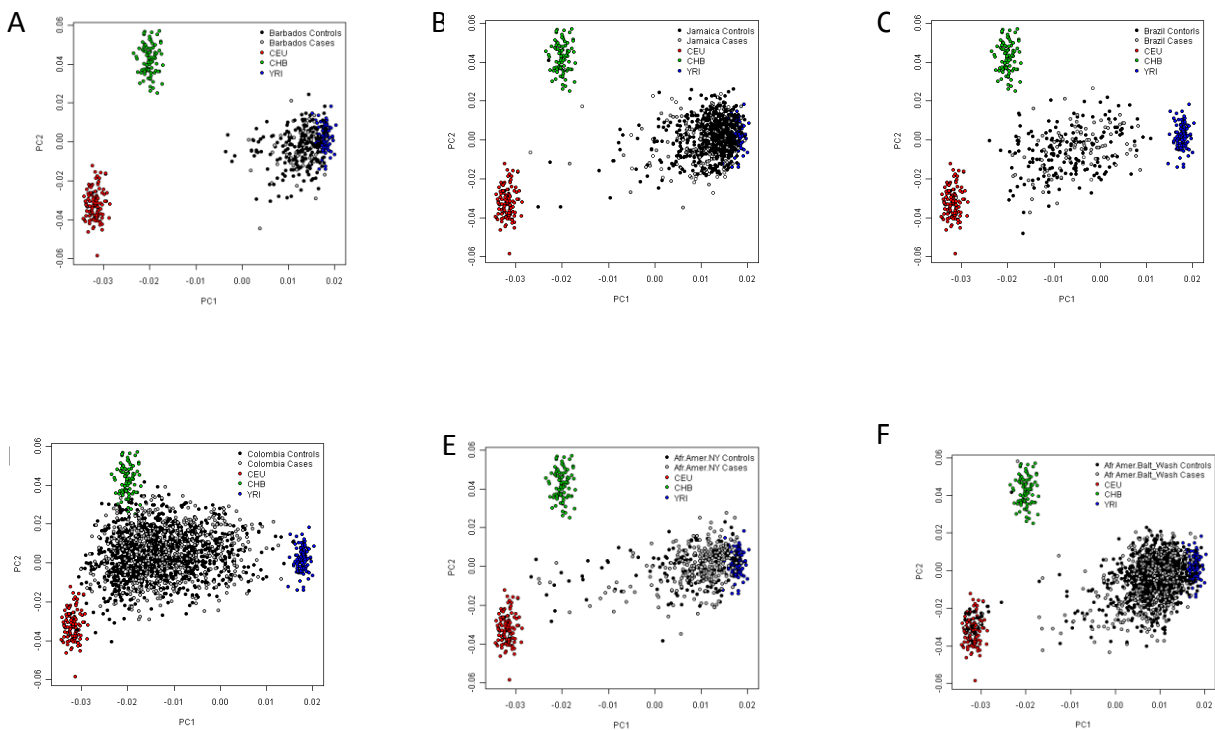


Figure 4. Meta-analytic forest plot of association of African ancestry and total IgE levels including Barbadians, Jamaicans, Brazilians, Colombians and African Americans of Baltimore Washington, D.C.

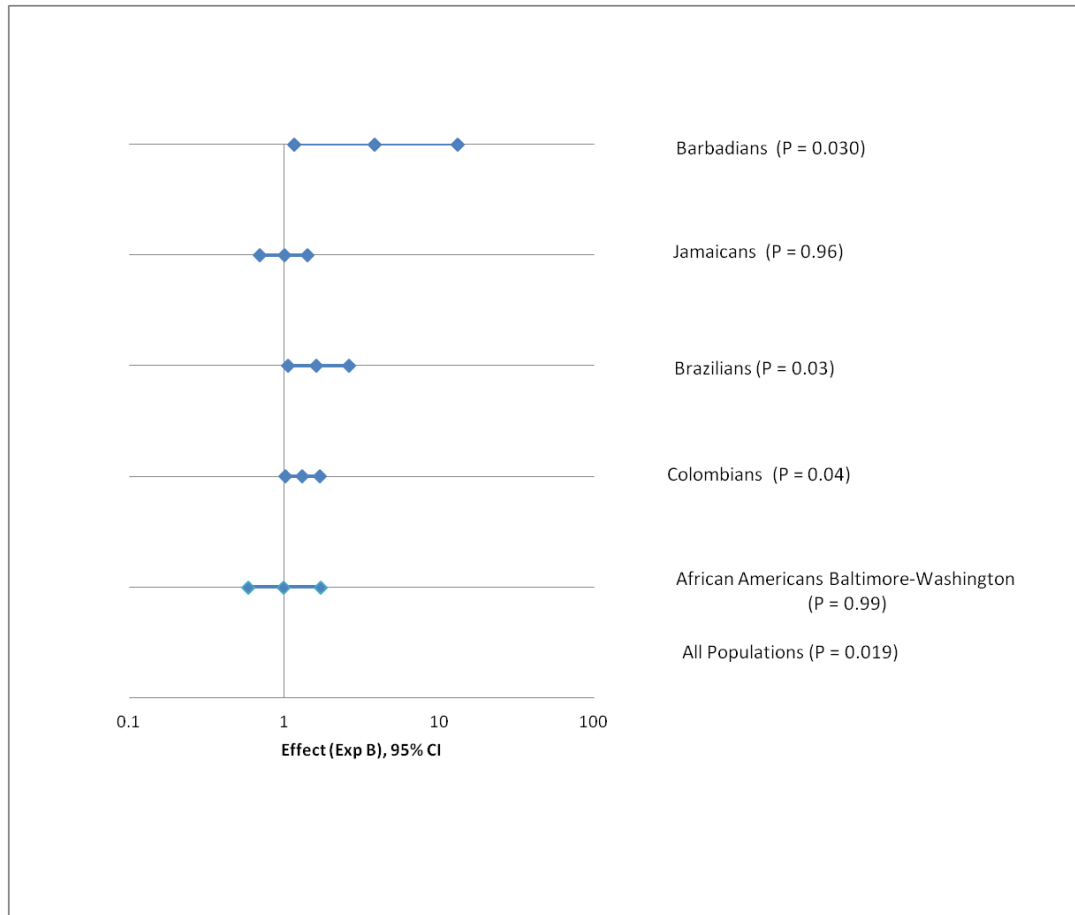
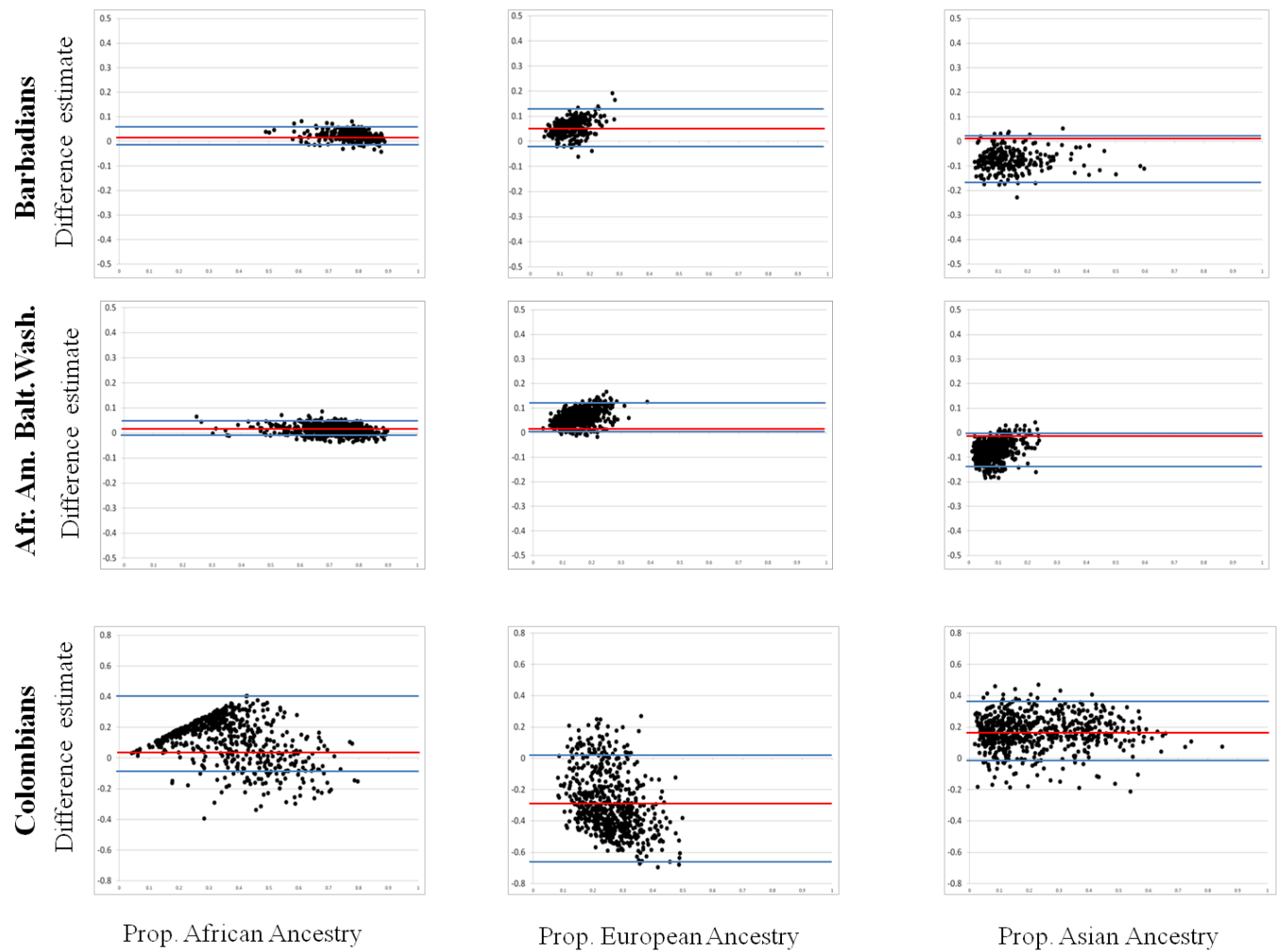


Figure 5. Bland-Altman plots showing error in individual ancestry estimates using the current panel of
AIMs to ancestral estimates using previous panels. The x-axis shows the ancestry estimate obtained using
the current panel ; the y-axis shows the difference in estimates between the current panel and a previous
panel of 416 AIMs in Barbadians and African Americans of Baltimore_Washington DC and 52 AIMs for
Colombians.



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