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Estimating African American Admixture Proportions by Use of Population-Specific Alleles

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Summary

We analyzed the European genetic contribution to 10 populations of African descent in the United States (Maywood, Illinois; Detroit; New York; Philadelphia; Pittsburgh; Baltimore; Charleston, South Carolina; New Orleans; and Houston) and in Jamaica, using nine autosomal DNA markers. These markers either are population-specific or show frequency differences >45% between the parental populations and are thus especially informative for admixture. European genetic ancestry ranged from 6.8% (Jamaica) to 22.5% (New Orleans). The unique utility of these markers is reflected in the low variance associated with these admixture estimates (SEM 1.3%–2.7%). We also estimated the male and female European contribution to African Americans, on the basis of informative mtDNA (haplogroups H and L) and Y Alu polymorphic markers. Results indicate a sex-biased gene flow from Europeans, the male contribution being substantially greater than the female contribution. mtDNA haplogroups analysis shows no evidence of a significant maternal Amerindian contribution to any of the 10 populations. We detected significant nonrandom association between two markers located 22 cM apart (FY-null and AT3), most likely due to admixture linkage disequilibrium created in the interbreeding of the two parental populations. The strength of this association and the substantial genetic distance between FY and AT3 emphasize the importance of admixed populations as a useful resource for mapping traits with different prevalence in two parental populations.

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Introduction

The history of African Americans can be traced back to 1619, when the first Africans arrived at the British colonies (Jamestown, Virginia), although the presence of African slaves has been reported as early as 1526 in Spanish expeditions to what would become South Carolina, Georgia, Florida, and New Mexico (Piersen 1996). Although institutional slavery began very soon after, it was not until the beginning of the 18th century that the importation of slaves reached significant rates, in parallel with the demand for workers to cultivate the tobacco, indigo, and rice plantations in the southern colonies. The highest peaks occurred during 1790–1800 and the first years of the 19th century. In 1808, slave trade became illegal but continued at a low rate for several more decades (Tanner 1995). Various estimates of the total number of slaves imported into the United States have been offered, with generally accepted numbers in the range 380,000–570,000 (Curtin 1969; Johnson and Campbell 1981). At present, >33 million U.S. residents are of African descent (U.S. Census Bureau).

Although it is very difficult to determine the precise ethnic origins of the African slaves, information from shipping lists has provided an approximate picture of their geographic provenance. The slave trade affected a very wide area of western and west central Africa, mainly the coastline between present-day Senegal in the north and Angola in the south. The most important regions were Senegambia (Gambia and Senegal), Sierra Leone (Guinea and Sierra Leone), Windward Coast (Ivory Coast and Liberia), Gold Coast (Ghana), Bight of Benin (from the Volta River to the Benin River), Bight of Biafra (east of the Benin River to Gabon), and Angola (southwest Africa, including part of Gabon, Congo, and Angola). Curtin (1969) has offered, on the basis of data on English trade during the 18th century (the peak of the Atlantic slave trade), estimates of the proportional contributions by areas. His analysis shows that Angola

and Bight of Biafra contributed the highest numbers of slaves imported into the North American mainland (~25% each). However, there were significant differences in ethnic origin depending on the port of entry in the United States, and the figures for the colonies of Virginia and South Carolina differed considerably.

The history of African Americans has been marked not only by the forced migration from Africa, but also by admixture with the other ethnic groups they met when they arrived in North America—namely, Europeans and Native Americans. Determination of the extent of that hybridization is of great anthropological, epidemiological, and historical interest. Unfortunately, although the first attempts to characterize admixture proportions in African Americans by means of genetic markers dates back to the 1950s (Glass and Li 1953), the field remains underdeveloped. The main limitations for obtaining precise admixture estimates have been the limited number of classical or DNA markers appropriate for this type of study and the scarcity of data concerning the distribution of allele frequencies in the parental populations, particularly in Africa. In the last few years, however, the number of dimorphic and hypervariable markers showing large frequency differentials between the major geographic or ethnic groups has increased substantially (Shriver et al. 1997). These markers, which we have designated "population-specific alleles" ("PSAs") are potentially very useful in forensic anthropology, epidemiology, and population genetics.

Recently, we initiated a project to systematically characterize admixture proportions in populations throughout the United States and in Jamaica, using autosomal PSAs. In this article we present data with regard to 10 populations of African descent from nine different areas of the United States and from Jamaica. Two of the markers we have used (FY-Null and ICAM) have alleles that are found only in persons with African ancestry, whereas eight (FY-Null, AT3, APO, GC, LPL, OCA2, RB2300 and Sb19.3) show differences in allele frequency >48% between Africans and Europeans. Using markers with unique alleles (those found in only one population; Chakraborty et al. 1992) and PSAs (those with high levels of allele frequency differential; Shriver et al. 1997), it is possible to generate more precise estimates of the ancestral proportions of an admixed population. In an effort to obtain the best possible estimates of the parental frequencies of these markers, we also analyzed three samples from Africa (two from Nigeria and one from Central African Republic) and three from Europe (England, Ireland, and Germany). We discuss the estimates of admixture in 10 populations of African descent in the context of the history of African American populations and previous genetic studies on admixture proportions in these groups. We also estimated the male and female European contribution to African Americans on the basis of mtDNA (haplogroups H and L) and Y Alu polymorphic (YAP) informative markers. To evaluate the extent of the Amerindian contribution to the African American gene pool, we looked for the presence of the Amerindian-specific mtDNA haplogroups (A, B, C, and D). Finally, we emphasize the importance of admixed populations in mapping disease genes showing prevalence differences between ethnic groups by taking advantage of the linkage disequilibrium created when populations hybridize.

Subjects and Methods

Subjects

The subjects analyzed in this study came from a number of sources, primarily paternity identity testing labs (the Detroit, Houston, and New Orleans samples), anthropological studies, and volunteers in medical studies. Table 1 shows the names of the populations analyzed and the number of individuals studied. The samples from Maywood (Illinois), Jamaica, and Nigeria-2 (from a traditional Yoruba community in the city of Ibadan, in southwestern Nigeria) were collected as healthy random subjects in an ongoing study of hypertension (see Ataman et al. 1996 and Cooper et al. 1997). The Nigeria-1 sample was collected from a group of civil servants in Benin City, Nigeria. The Central African Republic sample was collected as part of an anthropological survey of a village along the Oubangui river near the capital,

Table 1

Populations Analyzed in the Present Study

Population	*n*
Africans:	
Nigeria-1	46
Nigeria-2	100
Central African Republic	49
African Americans:	
Maywood, Ill.	100
Detroit	47
New York	93
Philadelphia-1	175
Philadelphia-2	126
Pittsburgh	84
Baltimore	96
Charleston, S.C.	94
New Orleans	105
Houston	100
Jamaicans	102
Europeans:	
England	44
Ireland	86
Germany	30
European Americans:	
Detroit	48
Pittsburgh	30
Louisiana (Cajuns)	47

Bangui. Related individuals were excluded from the sample. The New York sample comprised case and control subjects in an ongoing study of obesity in African Americans being conducted at Columbia University. Both samples from Philadelphia were collected as healthy control subjects during independent studies of hypertension in the African American population of Philadelphia. The Baltimore sample was collected as part of a study on the dynamics of HIV infection among intravenous drug users. The sample from Charleston was collected as part of a study on efforts for prenatal lead screening. All subjects in the Charleston sample were pregnant women. The samples of Europeans from Germany, Ireland, and England were collected at random as part of anthropological surveys.

Primer Sequences and PCR Conditions

The identified PSA markers were genotyped by standard PCR and electrophoretic separation of DNA fragments. Tables 2 and 3 show the sequences of the PCR primers and the reaction conditions for the autosomal PSA and sex-linked markers, respectively. Most of these markers are restriction site polymorphisms, which are detected by digestion with the appropriate restriction enzyme after PCR. All of these loci, except FY-Null and ICAM, were scored after electrophoresis through agarose gels. The fragments generated by the FY and ICAM digestions were smaller and required electrophoresis through polyacrylamide gels for accurate fragment sizing.

Statistical Analysis

The admixture proportions of the African American and European American populations were estimated by means of the weighted least squares (WLS) (Long 1991) and gene identity (Chakraborty 1975) methods. Long's method incorporates the effect of the evolutionary and sampling variance in the admixture estimates and a χ^2 test of heterogeneity of admixture estimates from the different loci. A computer program implementing this method (ADMIX.PAS) was kindly provided by Dr. Jeffrey C. Long (National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health). Dr. Ranajit Chakraborty (University of Texas Health Science Center, Houston) kindly provided a program (ADMIX2.FOR) for the estimation of admixture proportions by means of the gene identity method.

Haplotype frequencies and gametic disequilibrium coefficients for pairs of loci were estimated by means of an expectation maximization algorithm described by Long et al. (1995). Hypothesis testing was performed with the likelihood ratio statistic (G^2), which has a χ^2 distribution for large sample sizes. Alternatively, by a data-resampling approach, this program estimates the distribution of test statistics for the observed data given there was no association (Long et al. 1995). We used a simulated distribution based on 1,000 replications. A program (3LOCUS.PAS) implementing the aforementioned method was made available by Dr. Long. D′ coefficients, in which the gametic disequilibrium (D) is standardized by the theoretical maximum disequilibrium (D_{max}), were calculated on the basis of the estimated haplotype frequencies (Lewontin 1964, 1988; Thomson et al. 1988).

The fit of the genotype frequencies to the Hardy-Weinberg proportions was tested by Guo and Thomson's exact test (Guo and Thomson 1992) with the program ARLEQUIN 1.0 (Schneider et al. 1997), and the heterogeneity in the allele frequencies of the parental populations was analyzed by means of the STRUC program of the GENEPOP 2.0 computer package (Raymond and Rousset 1995).

Results

Admixture Estimates Based on Autosomal PSAs

Using nine autosomal PSA markers, we estimated the admixture proportions in samples from several populations of African descent. We also typed parental population samples from Africa (Nigeria and Central African Republic) and Europe (England, Ireland, and Germany) to verify the PSA status of the loci, to test for intracontinental heterogeneity, and to estimate the parental allele frequencies. Table 4 shows the allele frequencies estimated for the populations typed. All of the loci we used, except GC, are biallelic, and we show the frequency of the *1 allele, following the convention that the *1 allele corresponds to the larger band on the gel because of either the presence of an insertion or the absence of a restriction enzyme cut site. In Table 4, we also show the average of the parental allele frequencies for African and European populations and the levels of allele frequency differential for each marker. We detected no systematic deviations of the genotype frequencies with respect to the Hardy-Weinberg proportions in any population or marker (data not shown).

Table 5 summarizes the admixture results for the African American and Jamaican populations that we have analyzed. Shown is the city and state where the sample was collected and the proportion of European ancestry (m) in the population, obtained by two different methods to estimate admixture—the WLS method (Long 1991) and the gene identity method (Chakraborty 1975). The results of these methods are highly concordant ($r = 0.9949$, $P < .001$). The level of European admixture in these groups ranges from 6.8% in Jamaica to 22.5% in New Orleans. In the northern urban populations, we observed m values between 12.7% (Philadelphia) and

Table 2

Primer Sequences and PCR Conditions for the PSAs Typed in the Present Study

Locus	Type	Primer	DNA Sequence	PCR[a] (°C)	$MgCl_2$ (mM)	Notes	Reference
APO	Alu ins	APO4-F	AAGTGCTGTAGGCCATTTAGATTAG	94/50/72	2.0	1-minute extension	Batzer et al. 1996
		APO4-R	AGTCTTCGATGACAGCGTATACAGA				
AT3-I/D	68-bp ins/del	AT3id-F	CCACAGGTGTAACATTGTGT	94/55/72	2.0		Liu et al. 1995
		AT3id-R	GAGATAGTGTGATCTGAGGC				
GC	*Sty*I + *Hae*III	GC-F	AGATCTGAAATGGCTATTATTTTGC	94/55/72	2.0		Present study
		GC-R	GGAGGTGAGTTTATGGAACAGC				
FY-null	*Sty*I	P38	AGGCTTGTGCAGGCAGTG	94/55/72	1.0	No triton	Tournamille et al. 1995
		P39	GGCATAGGGATAAGGGACT				
ICAM-1	*Na*IIII	ICAM-F	CCCCTCAAAAGTCATCCTGC	94/60/72	1.5		Fernandez-Reyes et al. 1997
		ICAM-R	CATACACCTTCCGGTTGTTC				
LPL	*Pvu*II	LPL-R	AGGCTTCACTCATCCGTGCCTCC	94/60/72	1.5	0.1% triton	Gotoda et al. 1992
		LPL-L	TTATGCTGCTTTAGACTCTTGTC				
OCA2	*Hae*III	OCA2-10-F	CTTTCGTGTGTGCTAACTCC	94/60/72	2.5		Lee et al. 1995
		OCA2-10-R	ACCTCTAGCATGGTTCTTGGGC				
RB2300	*Bam*HI	RB2300-A	CAGGACAGCGGCCCGGAG	94/60/72	1.5	10% DMSO[b]	Bookstein et al. 1990
		RB2300-B	CTGCAGACGCTCCGCCGT				
Sb19.3	Alu ins	Sb19.3-F	TCTAGCCCCAGATTTATGGTAACTG	94/60/72	2.0	1-minute extension	Present study
		Sb19.3-R	AAGCACAATTGGTTATTTTCTGAC				

[a] PCR conditions: After an initial denaturation for 5 min at 94°C, DNA samples were amplified for 30 cycles at the denaturation/annealing/extension temperatures specified for each marker, followed by a final extension for 5 min at 72°C. Unless otherwise indicated, denaturation, annealing, and extension times were 30 s. Amplifications were performed in a 25-μl reaction volume containing 200 μM dNTPs, 10 mM Tris-HCl (pH 8.9), 50 mM KCl, 0.1% Triton X-100, 1 U *Taq* polymerase, and 20 ng genomic DNA.

[b] DMSO = dimethyl sulfoxide.

Table 3

Primer Sequences and PCR Conditions for the mtDNA and Y Chromosome Polymorphisms Typed in the Present Study

Locus	Type	Primer	DNA Sequence	PCR[a] (°C)	$MgCl_2$ (mM)
mtDNA					
HAP-L	*Hap*I	3457-F	GACGCCATAAAACTCTTCAC	94/55/72	1.5
		3661-R	TCAGAGGATTGAGTAAACGG		
HAP-H	*Alu*I	6960-F	CTGACTGGCATTGTATTAGC	94/55/72	1.5
		7117-R	AGGGTGTAGCCTGAGAATAG		
HAP-A	*Hae*III	577-F	GTTTATGTAGCTTACCTCCTC	94/55/72	1.5
		743-R	GATCGTGGTGATTTAGAGGGTG		
HAP-B	9-bp ins	8195-F	ATGCTAAGTTAGCTTTACAG	94/50/72	2.0
		8317-R	ACAGTTTCATGCCCATCGTC		
HAP-C	*Hin*eII	13208-F	CGCCCTTACACAAAATGACATCAA	94/55/72	2.0
		13413-R	ATTTTTCGAATATCTTGTTC		
HAP-D	*Alu*I	5099-F	CCTAACTACTACCGCATTCCTAC	94/50/72	2.0
		5274-R	CTTCGATAATGGCCCATTTGGGC		
Y chromosome					
YAP	Alu Seq	YAP-1	CAGGGGAAGATAAAGAAATA	94/55/72	2.0
		YAP-2	ACTGCTAAAAGGGGATGGAT		

[a] PCR conditions: After an initial denaturation for 5 min at 94°C, DNA samples were amplified for 30 cycles at the denaturation/annealing/extension temperatures specified for each marker, followed by a final extension for 5 min at 72°C. Denaturation, annealing, and extension times were 30 s. Amplifications were performed in a 25-μl reaction volume containing 200 μM dNTPs, 10 mM Tris-HCl (pH 8.9), 50 mM KCl, 0.1% Triton X-100, 1 U *Taq* polymerase, and 20 ng genomic DNA.

20.2% (Pittsburgh). It is important to note that two independent samples from African Americans living in Philadelphia point to a relatively low European contribution (12.7% and 13.8%, respectively). Southern African Americans show a wide range of European influence, from 11.6% (Charleston) to 22.5% (New Orleans), the lowest and highest values, respectively, observed for the U.S. populations we analyzed. Finally, the sample from Jamaica shows evidence of a much lower European genetic contribution (6.8%) than that found in any of the African American populations. The variance associated with the admixture estimates is very low for all the populations studied. By Long's method, which incorporates the effect of the evolutionary and sampling variance in the admixture estimates, the standard errors range between 1.3% (Charleston and Jamaica) and 2.7% (Detroit).

We also tested for heterogeneity in the individual locus admixture estimates within the populations sampled. The χ^2 test showed no evidence of significant heterogeneity in any of the populations (data not shown), and we observed no systematic deviations for any of the loci and therefore no evidence of the action of natural selection in the markers considered in the present analysis.

Admixture Estimates Based on mtDNA and Y Chromosome Data

We analyzed these 10 African American and Jamaican samples for the presence of six population-specific mtDNA haplogroups (L, H, A, B, C, and D) and the YAP element. The relevant data are summarized in Table 6. L and H are the most common haplogroups that are unique to African and European populations, respectively (Torroni et al. 1994, 1996; Chen et al. 1995), and can be used to test the relative African and European maternal contribution to African Americans and Jamaicans. The first two data columns of Table 6 indicate the *m* values based on the L and H haplogroups, and, in the third data column, we indicate the average mtDNA value. The European maternal contribution is lower than the average estimate obtained for the nine autosomal markers analyzed in this study (see Table 5).

Haplogroups A, B, C, and D are Amerindian-specific haplogroups that together account for almost all Amerindian mtDNAs (Wallace and Torroni 1992) and are thus especially suitable for testing the importance of the Amerindian influence in the African American maternal line. Of the >1,000 African Americans analyzed, we detected only 4 individuals with an Amerindian haplogroup. Two individuals in Maywood, one in Baltimore, and one in Houston showed the Amerindian B haplogroup. Several other samples have the 9-bp deletion, but since it appears to be associated with the L African haplogroup and lacks the characteristic pattern observed in Amerindian B haplogroups for the diagnostic sites *Dde*I 10394 and *Alu*I 10397 (−−), it is most likely of African origin (Soodyall et al. 1996).

The YAP marker (Hammer 1994) is very useful for the characterization of the male European contribution, given the difference in frequency of the Alu insertion

Table 4

Allele Frequencies of the Autosomal PSAs Analyzed

Population	APO*1	AT3*1	FY-NULL*1	ICAM*1	LPL*1	OCA2*1	RB2300*1	Sb19.3*1	GC-1F	GC-1S
Africans										
Nigeria-1	.409	.889	.000	.772	.957	.078	.917	.457	.849	.081
Nigeria-2	.480	.875	.000	.697	.985	.124	.944	.455	.846	.085
Central African Republic	.435	.859	.000	.798	.978	.092	.900	.364	.778	.067
African average	.441	.874	.000	.756	.973	.098	.920	.425	.824	.078
Europeans										
England	.934	.291	1.000	1.000	.528	.695	.294	.949	.203	.622
Ireland	.915	.279	1.000	1.000	.397	.761	.287	.943	.133	.633
Germany	.933	.267	1.000	1.000	.533	.850	.417	.839	.133	.567
European average	.927	.279	1.000	1.000	.486	.769	.333	.910	.156	.607
$\Delta(\lvert pafr-peur \rvert)$	.486	.595	1.000	.244	.487	.671	.588	.485	.668	.529
African Americans										
Maywood, Ill.	.520	.770	.185	.795	.848	.203	.776	.465	.710	.177
Detroit	.533	.818	.133	.798	.878	.207	.849	.659	.722	.200
New York	.522	.668	.210	.755	.890	.220	.821	.557	.738	.146
Philadelphia-1	.494	.767	.149	.750	.911	.153	.851	.524	.795	.125
Philadelphia-2	.504	.774	.160	.750	.911	.137	.802	.467	.771	.169
Pittsburgh	.551	.747	.217	.768	.845	.253	.807	.500	.743	.129
Baltimore	.505	.727	.141	.859	.872	.156	.855	.552	.779	.176
Charleston, S.C.	.500	.770	.112	.777	.931	.208	.888	.522	.765	.133
New Orleans	.593	.727	.200	.829	.865	.284	.842	.550	.669	.215
Houston	.525	.742	.188	.753	.890	.208	.802	.440	.744	.148
Jamaicans	.511	.810	.065	.742	.935	.091	.870	.522	.790	.113
European Americans										
Detroit	.935	.271	.990	1.000	.365	.854	.344	.938	.181	.564
Pittsburgh	.917	.350	.983	1.000	.417	.817	.283	.897	.172	.569
Louisiana (Cajuns)	.935	.239	.989	1.000	.500	.691	.350	.922	.106	.628

NOTE.—We have followed the convention of defining the presence of Alu insertions and the absence of the polymorphic restriction sites as allele 1, the exception being the GC locus, where we have named alleles using the allelic designations of the protein-based assays.

between Europeans and Africans (>80%). The *m* estimates are also indicated in Table 6. The male European contribution is substantially higher than the female contribution in every population, as is evident from the estimated *m* values obtained for YAP and mtDNA.

Demonstration of Admixture Linkage Disequilibrium between Two Markers 22 cM Apart

Two of the PSA markers used to estimate admixture (FY and AT3) are located in the same chromosomal band. In fact, mapping data show that FY and AT3 are linked at a distance of ~22 cM (male distance = 18 cM and female distance = 23 cM [Cooperative Human Linkage Center, Genetic Location Database]). We created pairwise haplotypes of FY and the other eight loci to test whether there is detectable linkage disequilibrium between FY and AT3 or between FY and any of the other PSAs typed. Haplotype frequencies were estimated by means of the expectation maximization algorithm as implemented in a program provided by Dr. Long (1995). This method has proved capable of generating very accurate estimates of multilocus haplotype frequencies without families. Table 7 shows the level of D′, the likelihood ratio statistic, and the corresponding *P* value for significant results. A positive D′ indicates a higher-than-expected frequency of haplotypes with both African-specific alleles, and a negative D′ indicates the combination of a European allele in one locus with an African allele in the other locus. In the case of the haplotype frequencies of FY and AT3, a positive disequilibrium is consistently found in all the African American populations (with the exception of Maywood, which is in equilibrium), and in 6 of the 10 populations (New York, Baltimore, Charleston, New Orleans, Houston, and Ja-

Table 5

Estimated European Ancestral Proportions of 11 Populations of African Descent

Population	WLS	Gene Identity
Maywood, Ill.	18.8 ± 1.4	18.2 ± 0.5
Detroit	16.3 ± 2.7	16.9 ± 0.8
New York	19.8 ± 2.1	20.2 ± 0.2
Philadelphia-1	12.7 ± 1.5	12.6 ± 0.0
Philadelphia-2	13.8 ± 1.9	13.2 ± 0.3
Pittsburgh	20.2 ± 1.6	20.1 ± 0.4
Baltimore	15.5 ± 2.6	15.4 ± 0.8
Charleston, S.C.	11.6 ± 1.3	12.2 ± 0.2
New Orleans	22.5 ± 1.6	22.8 ± 0.5
Houston	16.9 ± 1.5	16.6 ± 0.6
Jamaica	6.8 ± 1.3	7.4 ± 0.2

Table 6

African American and Jamaican Ancestral Proportions Determined by Using mtDNA and Y PSAs

Population	HAP-L (%)	HAP-H (%)	mtDNA (%)	YAP (%)
Maywood, Ill.	16.61	.00	8.31	24.32
Detroit	−.01	.00	.00	30.33
New York	18.23	.00	9.11	18.58
Philadelphia-1	8.12	13.93	11.02	22.94
Philadelphia-2	.03	5.66	2.84	23.55
Pittsburgh	11.24	8.56	9.90	23.87
Baltimore	24.89	4.99	14.94	22.79
Charleston, S.C.	12.92	.00	6.46	NA
New Orleans	10.75	3.33	7.04	46.88
Houston	10.97	2.64	6.80	8.55
Jamaica	25.86	.00	12.93	17.89

NOTE—One individual from Baltimore, one from Houston, and two from Chicago had one of the Amerindian haplogroups (Hap B). NA = not available; only females in the sample.

maica) there are significant differences with respect to the expected frequencies. With the Bonferroni correction for multiple tests ($\alpha = 0.005$), the deviations are still significant in two populations (New York and New Orleans, $P < .001$) and border on significance in Baltimore ($P = .006$). We constructed haplotypes of the other seven loci with FY to test whether the significant association observed between FY and AT3 is truly a function of the linkage between these two markers or is the result of genomewide association among informative PSA markers due to substructure. In these comparisons we observe both positive and negative D′ values, and only 7 of the 70 tests show significant deviations. After the Bonferroni correction for multiple tests, none of the deviations were significant.

Discussion

Admixture in African American and Jamaican Populations

We have estimated the admixture proportions in 10 populations from different geographic areas in the United States and Jamaica, using a set of very informative autosomal markers. These values can be compared with those reported in the literature (Table 8). Our estimate for the Pittsburgh sample (20.2% ± 1.6%) is not significantly different from the one obtained by Chakraborty et al. (1992) for the same population (25.2% ± 2.7%), employing the identical statistical method (Long's WLS method). The *m* value for New York (19.8%) is also consistent with previously reported estimates (18.9%; Reed 1969). However, there are also several discrepancies with respect to data published elsewhere. Our estimate for Baltimore (15.5%) does not seem to agree with the estimates based on Rh, GM, and FY (Glass and Li 1953; Glass 1955; Workman 1968; Reed 1969), >20% in all cases. A similar situation is observed in the sample from Detroit, which shows a lower level (16.3%) in the present study than in previous studies (26%, Reed 1969). With respect to the southern populations, our *m* value for Charleston (11.6%) is slightly higher than previous estimates (4%–8%, Workman 1968). There are no data concerning the other populations included in this analysis (Maywood, Philadelphia, New Orleans, Houston, and Jamaica).

Previous studies have indicated that northern U.S. populations show a higher level of European ancestry than do southern U.S. populations. Nevertheless, the results of the present study seem to indicate that the situation is much more complex than previously thought. There appears to be a significant degree of variation in the admixture level of northern populations (from 13% in Philadelphia to 20% in Pittsburgh). It is also clear that, in general, the European ancestry of northern African American populations is somewhat lower than previous reports have described. The agreement of estimates based on independent African American population samples from Philadelphia is notable and strengthens the support for the accuracy of these estimates.

The three southern African American populations (New Orleans, Houston, and Charleston) show a wide range of admixture values (11.6%–22.5%). The Charleston population is of special interest because data on admixture proportions in African Americans from the former southern British colonies (South Carolina and Georgia) have been used to postulate differences in gene flow between the northern and southern African American populations. The population of Charleston shows the lowest *m* value (11.6%) of all the U.S. populations analyzed in the present study, but it is not very different from the estimates of one of the northern African American populations—namely, Philadelphia. It would be very interesting to have data on additional samples of southern African American populations to confirm the existence of a low European contribution in this particular area and to study the extent of heterogeneity in the admixture proportions at this geographical level.

One explanation for the lower-than-expected and heterogeneous levels of European admixture in the urban northern African Americans can be formed on the basis of the demographic history of African American populations. In the period after World War I, there were significant changes in the distribution of African Americans in the United States. In the largest internal migration in the history of North America, southern African Americans, constituting the immense majority (~90%) of the total African American population, left the rural South in search of new opportunities in the urban areas of the North. It is known that big cities such as Chicago, Detroit, New York, Philadelphia, Pittsburgh, and Bal-

Table 7

Levels of Linkage Disequilibrium for Haplotypes of FY and the Four Other PSAs Typed

	AT3			APO			ICAM			LPL			OCA2			RB2300			Sb19.3			GC		
Population	D′ (%)	G	*P*	D′ (%)	G	*P*	D′ (%)	G	*P*	D′ (%)	G	*P*	D′ (%)	G	*P*	D′ (%)	G	*P*	D′ (%)	G	*P*	D′ (%)[a]	G	*P*
Maywood, Ill.	−.2	.00	NS	14.0	.42	NS	−16.1	.15	NS	−96.8	2.48	NS	12.2	1.27	NS	4.2	.15	NS	−19.8	.79	NS	−2.7	.03	NS
New York	59.0	20.63	<.001	−3.2	.03	NS	2.1	.05	NS	12.3	3.09	NS	10.2	1.08	NS	8.7	1.27	NS	32.0	2.14	NS	9.6	1.11	NS
Philadelphia-1	18.0	2.31	NS	31.8	2.49	NS	−13.6	.11	NS	.4	.00	NS	.9	.01	NS	−1.9	.00	NS	−11.0	.29	NS	36.8	10.31	.002
Philadelphia-2	8.5	.57	NS	41.3	4.23	.041	31.8	5.69	.024	−99.3	1.83	NS	5.4	.22	NS	−10.9	.06	NS	−32.0	2.50	NS	−21.6	.21	NS
Pittsburgh	1.3	.02	NS	7.3	.13	NS	1.4	.02	NS	16.1	3.02	NS	−8.4	.05	NS	−37.2	1.22	NS	14.5	.56	NS	11.9	1.68	NS
Baltimore	44.3	8.39	.006	20.8	.67	NS	1.3	.02	NS	21.4	4.58	.027	13.4	1.25	NS	−13.3	.05	NS	59.8	5.68	.030	38.6	7.33	.023
Charleston, S.C.	40.8	5.22	.024	23.6	.61	NS	−64.5	2.34	NS	−100.0	1.32	NS	16.5	1.16	NS	3.9	.11	NS	12.8	.16	NS	14.4	1.48	NS
New Orleans	46.0	18.86	<.001	22.1	1.32	NS	−13.4	.14	NS	3.9	.30	NS	34.0	8.24	.006	6.4	.74	NS	32.4	3.04	NS	28.8	4.77	NS
Houston	26.8	4.29	.049	37.1	2.58	NS	−56.7	3.13	NS	9.3	1.56	NS	15.4	1.66	NS	−33.8	.73	NS	30.8	3.14	NS	30.3	.72	NS
Jamaica	50.6	5.99	.008	11.1	.09	NS	−7.8	.01	NS	4.4	.15	NS	−20.3	.02	NS	25.6	2.58	NS	−49.1	2.02	NS	21.6	2.75	NS

NOTE.—Detroit has been excluded because of small sample size.

[a] D′ value corresponding to the GC-1F allele.

Table 8

European Genetic Contribution to African American and Jamaican Populations Analyzed

Population and Reference	*m*
Non-Southern	
Detroit	
Reed (1969)	26.0
Present study	16.3 ± 2.7
Maywood, Ill.	
Present study	18.8 ± 1.4
New York	
Reed (1969)	18.9
Present study	19.8 ± 2.1
Philadelphia	
Present study (Philadelphia-1)	12.7 ± 1.5
Present study (Philadelphia-2)	13.8 ± 1.9
Pittsburgh	
Chakraborty et al. (1992)	25.2 ± 2.7
Present study	20.2 ± 1.6
Baltimore	
Glass and Li (1953)	30.6
Glass (1955)	21.6
Present study	15.5 ± 2.6
Oakland	
Adams and Ward (1973)	21.9
Southern	
Charleston, S.C.	
Workman (1968)	4–8
Adams and Ward (1973)	4
Present study	11.6 ± 1.3
Claxton, Ga.	
Long (1991)	13.6 ± 5.1
Sapelo Island, Ga.	
Long (1991)	6.8 ± 5.5
James Island, S.C.	
Adams and Ward (1973)	15.3
Evans and Bulock, Ga.	
Workman et al. (1963)[a]	10.4
Blumberg et al. (1964)[a]	7.3
New Orleans	
Present study	22.5 ± 1.6
Houston	
Present study	16.9 ± 1.5
Jamaica	
Present study	6.8 ± 1.3

[a] From Chakraborty (1986).

timore experienced a very significant increase in the number of African American residents, both in absolute and in relative terms (Johnson and Campbell 1981; Tanner 1995). Given the existence of a North/South cline in admixture proportion, the reason for the lower European admixture observed in particular populations may be due to more recent immigrants from the rural South. Unfortunately, we have no data concerning the geographic origin of the individuals in any of our samples, so there is no direct way to test this hypothesis. Further knowledge of the European genetic contribution to African American populations from additional southern states that greatly contributed to the "Great Migration" (the cotton belt states—Mississippi, Alabama, and Georgia) and the availability of northern samples with family demographic information would be important to clarify this point.

In any case, our study shows that not all the southern African American populations have as low a European genetic contribution as that found in the Charleston sample. The estimate for Houston (16.9%) is similar to other values observed in northern urban populations (Detroit and Baltimore), and New Orleans shows the highest *m* value of the cities studied (22.5%), which deserves special attention. The history of the Louisiana territory has been quite different from the history of other southern regions in the United States. This area was under French rule for a substantial period, until it became part of the Spanish territory in 1763 and, finally, of the United States some decades later, in 1803. Both the geographic origin of the slaves imported to Louisiana and their status during the French domination have been distinct from what happened in the southern British colonies (e.g., South Carolina). There have been historical accounts of more substantial intermixture in the New Orleans area (Williamson 1995; Piersen 1996), so this could partly explain the observed differences in ancestral proportions between Charleston and New Orleans.

Finally, we also characterized the European admixture in a sample from Jamaica, which shows a very low *m* value (6.8%). Further studies of Caribbean populations of African ancestry are needed to confirm this low European genetic contribution.

The standard errors of the estimates are very small, ranging from 1.3% (Charleston and Jamaica) to 2.7% (Detroit). It is not possible to directly compare the magnitude of the standard errors of our estimates with those of many of the classical estimates in the literature, which were based mainly on single markers and used a different statistical methodology (in which only the sampling error, but not the evolutionary error, was taken into account). However, we may use as a reference the paper of Chakraborty et al. (1992), in which Long's WLS method was used to analyze data on 52 alleles at 15 protein-coding loci in a sample of African Americans living in Pittsburgh. All of our estimates have a lower associated standard error (2.7%) than that reported by Chakraborty et al. (1992). This comparison stresses the importance of an appropriate selection of markers for a precise estimate of the admixture proportions. Another critical factor for admixture estimation is the representative parental population samples that are available. An inadequate selection of parental populations may seriously bias estimates of admixture. An interesting example is the well-known estimate of Glass and Li (1953) of the European gene contribution to the Baltimore population on the basis of the Rh system. The original estimate was 31%, which, in light of new data on African

frequencies, was revised, 2 years later, to 22% (Glass 1955). We have typed three African samples (two from Nigeria and one from Central African Republic) and three European samples (from Great Britain, Ireland, and Germany) to estimate the parental frequencies. The aforementioned populations contributed substantially to the origin of the African American populations. These African populations are reasonably good representatives of the populations involved in the slave trade that affected a wide area of western and west central Africa. In addition, none of the markers we tested show any evidence of heterogeneity in the gene frequencies of the three samples representative of the African parental populations, which minimizes the possibility of introducing bias due to the unequal contributions of the different slave areas to the original populations of African descent living in the United States. With respect to the European samples, England, Ireland, and Germany have been main sources for the European migration to North America (Tanner 1995). Other relevant areas of Europe (e.g., Italy) are not represented in this study, but, given the known genetic homogeneity of the European populations, it is unlikely that this would affect the admixture estimates in any significant way. Supporting this is the fact that the gene frequencies of the three European American populations analyzed here are very similar to the European average frequencies (Table 4). The European samples also show homogeneity for the gene frequencies of almost all markers, with the exception of LPL and Sb19.3.

In addition to the data on the autosomal markers, further insight on the nature and dynamics of admixture may be obtained by using maternally and paternally transmitted markers (mtDNA and the nonpseudoautosomal region of the Y chromosome, respectively). The results of this analysis strongly indicate a sex-biased European contribution, in contradiction with the only other information available to date (Hsieh and Sutton 1992). In every population there is evidence of a higher European male contribution, as indicated by the *m* values obtained for YAP and mtDNA. Therefore, even if marriages between African American men and European American women are currently more common than marriages between African American women and European American men (see, e.g., Wilkinson 1975 and Piersen 1996), it seems clear that during a substantial part of African American history, men of European descent have made a more significant genetic contribution to the African American gene pool than have women of European descent. This is in accordance with the historical data regarding the period of slavery in the United States (Williamson 1995).

We have also tried to clarify the extent of the Amerindian contribution to the African American gene pool. There have been accounts of substantial contact among North American Indians and people of African descent in specific periods of U.S. history, especially in regions such as the Mississippi delta and Florida (Katz 1986). Some early anthropological reports have emphasized the high proportion of African American college students claiming some Amerindian ancestry (Herskovits 1930; Meier 1949). In fact, the importance of the Amerindian contribution to the African American gene pool has been a matter of controversy since the first studies of African American admixture (Roberts 1955; Glass 1955). However, practically all admixture studies of African American populations to date have employed a dihybrid model (African/European) instead of a trihybrid model (African/European/Amerindian). We tested our African American samples for the presence of the common Amerindian-specific mtDNA haplogroups (A, B, C, and D), and detected just 4 individuals with an Amerindian haplogroup, among >1,000 African Americans. This indicates that the contribution from Amerindians has been of little importance in the 10 populations of African descent we have characterized, at least on the maternal line.

We also determined the extent of the African contribution to three European American populations from several areas in the United States: Detroit, Pittsburgh, and Louisiana (Cajuns). The presence of the FY null allele in the three populations clearly indicates an introgression of African genes into the European American gene pool, but the African contribution globally seems to have been very limited, ~1% (mean ± SEM: Detroit 0.5% ± 0.7%; Pittsburgh 1.2% ± 0.9%; and Cajuns 0.7% ± 0.6%).

Application of Admixed Populations for Mapping Disease Genes

In the last few years, interest in admixed populations has been increasing. In 1988, Chakraborty and Weiss described a new method for mapping disease genes, using admixed populations. This method is based in the linkage disequilibrium created when two ethnically distinct populations hybridize, and it should be very useful for mapping disease genes showing high prevalence differences among the parental populations. Non–insulin-dependent diabetes mellitus and obesity (disproportionately common among Hispanics and African Americans), hypertension (among African Americans), lung and prostate cancer (among African Americans), and other anthropological traits could be studied by this method. Stephens et al. (1994) and Briscoe et al. (1994) further extended the work of Chakraborty and Weiss 1988, using computer simulations, and introduced the acronym "MALD" (mapping by admixture linkage disequilibrium) to designate this method. Their results indicated that, using sample sizes of 200–300 patients,

typed for 200–300 evenly spaced markers, each having >30% frequency difference between the parental populations, one would have a >95% chance of locating the causative gene. Our own simulations (unpublished data) show that microsatellites would be as informative as dimorphic markers for MALD studies. It has also been proposed by McKeigue (1997) and Kaplan et al. (1997) that the linkage disequilibrium that results from recent admixture could also be used to detect disease genes for qualitative or quantitative traits by means of the transmission disequilibrium test (Spielman et al. 1993; Allison 1997). The aforementioned theoretical studies predict that linkage disequilibrium would be detectable in admixed populations even between relatively distant markers (10–20 cM). As described above, we detected a significant nonrandom association between two of the PSAs analyzed in the present study: FY-null and AT3, located on the large arm of chromosome 1 at a distance of 22 cM. The most likely explanation is that this association is the result of admixture linkage disequilibrium that was generated through the hybridization of the parental populations of these African American populations and has persisted, extending over a distance of 22 cM. Population substructure could also potentially result in nonrandom associations among such PSA loci. However, if this were the cause of the FY/AT3 associations observed in these populations, we would expect to detect a higher number of significant associations for the other seven loci and would also expect to observe deviations from Hardy-Weinberg equilibrium. This observation of a significant linkage disequilibrium over such long distances as a result of admixture is encouraging, and it emphasizes the utility of admixed populations as an important resource for mapping disease genes.

Conclusions

The present study indicates that the admixture process that began with the arrival of the first Africans at the British colonies >250 years ago has been very complex. Even if our data tend to corroborate the existence of differences in the extent of European contribution to southern and nonsouthern African Americans, it seems that recent demographic processes that have dramatically changed the distribution of African Americans in the United States have substantially altered the global picture. Of special importance has been the Great Migration, a massive movement of African Americans from the rural areas in the South to the urban areas in the North, which took place after the World War I. Thus, it is possible that the differences in the admixture proportion observed among African American samples in northern cities is a consequence of the different percentages of African Americans of southern origin currently living in those areas. In addition, the substantial differences in the histories of the diverse areas of the United States may account for the variation observed in the admixture proportions. Such seems to be the case for New Orleans, which shows a much higher European contribution than that found in Charleston.

Admixed populations are an important resource that can and should be used to study the genetics of complex disease. A prerequisite to this application is a better understanding of the admixture proportions and dynamics of the admixture process. We have established a panel of genetic markers that have high levels of allele frequency differential between the parental populations and low levels of heterogeneity within continents. We propose that these markers could serve as a core marker panel for future studies of admixture in additional population samples. It is notable that most of these markers also show substantial frequency differences between African and Amerindian populations (data not shown) and should thus also be useful for estimating the African contribution to U.S. Hispanic and Amerindian populations. Use of a common set of informative markers for studies of admixture will make it possible to compile data from a number of populations and laboratories to construct a U.S. admixture map.

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Electronic-Database Information

URLs for data in this article are as follows:

Cooperative Human Linkage Center, http://www.chlc.org (for mapping data regarding FY and AT3)
Genetic Location Database, http://cedar. genetics.soton.ac.uk/public_html (for mapping data regarding FY and AT3)
U.S. Census Bureau, http://www.census.gov (for percentage of Americans of African descent)

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