Using Genetic Admixture to Explain Racial Differences in Insulin-Related Phenotypes

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Documented differences in measures of insulin secretion and action between African Americans and European Americans may be due to either genetic or environmental factors. This study used genetic admixture (ADM), determined from ~20 ancestry informative markers, and a questionnaire designed to assess socioeconomic status (SES) to examine potential genetic and environmental contributions to minimal model–derived measures of insulin sensitivity (S_I), fasting insulin, and the acute insulin response to glucose (AIR_g) in 125 children residing in Birmingham, Alabama. The study was longitudinal in design and yielded multiple outcome measures on each subject. Mixed models analysis was used to determine if ADM and SES were independently related to S_I, fasting insulin, and AIR_g after adjusting for confounding factors (pubertal status, adiposity, age) and for repeated testing of individuals. In this cohort, African ADM ranged from 0% (individuals with no markers reflecting African ancestry) to 100% (individuals with all 20 markers reflecting African ancestry). Results indicated that ADM was independently related to S_I ($P < 0.001$) and fasting insulin ($P < 0.01$), with individuals having greater African ADM having a lower S_I and a higher fasting insulin concentration. Both ADM ($P < 0.001$) and SES ($P < 0.05$) were independently related to AIR_g; children with greater African ADM or lower SES had a higher AIR_g, even after adjusting for S_I. These observations suggest that use of ADM can replace assignment of individuals to categorical racial groups; that lower S_I and higher fasting insulin among African Americans compared with European Americans may have a genetic basis; and that higher AIR_g among African Americans may be due to both genetic factors and to environmental factors that remain to be identified.
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ADM, genetic admixture; AIR_g, acute insulin response to glucose; SES, socioeconomic status; S_I, insulin sensitivity.

Differences in measures of insulin secretion and action between African Americans and European Americans have been identified in the literature (1–6). These differences were identified by using self-identified "race" as an independent variable in statistical models. However, because race is a combination of both genetic and environmental factors, the basis for racial differences in aspects of physiology and metabolism is not clear.

One way to investigate putative genetic factors contributing to racial differences in complex physiological traits such as insulin sensitivity (S_I) is by use of genetic admixture (ADM) analysis. ADM analysis is an extension of the "Mapping by Admixture Linkage Disequilibrium" approach. In general terms, the admixture approach takes advantage of the allelic variation produced by the intermixing of long-separated parental populations. In the U.S., this process was initiated during the European colonial period, which was extended to the New World in 1492, and resulted in a number of admixed populations (African Americans, and Hispanics and Latinos of North and South America). The combination of allelic variants in an individual that corresponds to each parental population considered is translated into a quantitative value. The ADM value reflects a portion of the biological ancestral determinants that influence an individual's racial identity. It can also be thought of as the estimated proportion of an individual's genome that is of a given ancestral origin (e.g., African) based on the specific markers used for the analysis.

The ADM approach provides a useful means to avoid assignment of individuals of mixed ethnic descent into categorical racial groups. The ADM approach also has potential value in identifying genes that confer disease risk. If a given allelic variant is associated with altered risk for a given disease, then this variant can ultimately be used as a mapping tool to identify genes associated with physiological outcomes that affect disease risk. The application of the ADM approach to mapping genes associated with variation in complex traits has been discussed elsewhere (7–10).

In the present study, individual values of ADM were used to explore the extent to which ancestral biological determinants explained racial differences in insulin-related phenotypes previously reported in the literature (1–6). A quantitative value representing ADM was obtained after genotyping African-American and European-American children at ~20 markers informative for parental ancestry. These ADM values were then examined for

their association with measures of S_I, fasting insulin concentration, and the acute insulin response to glucose (AIR_g). The specific hypothesis tested was that ADM, which represents the genetic contribution of race, and socioeconomic status, an index of the environmental contribution of race, would explain unique portions of variance in S_I, fasting insulin, and AIR_g. This approach—i.e., quantitative use of ADM values—has not been used previously to examine racial/ethnic differences in aspects of insulin secretion and action.

RESEARCH DESIGN AND METHODS

Subjects. Of the 125 children included in the study, 52 identified themselves as African American (23 boys; 29 girls), and 73 as European American (26 boys; 47 girls). Individuals were considered to be of a given ethnic/racial group if both parents and all grandparents were of the same ethnicity/race as the child. The age range of the subjects was 5–16 years. All subjects were recruited as part of a longitudinal study exploring the contribution of body fat distribution to disease risk. Recruitment of study subjects has been explained elsewhere (6). Only individuals for whom ADM could be determined (from whom genetic material was obtained) were included in the study. The study was in compliance with the regulations of the Institutional Review Board at the University of Alabama at Birmingham.

Study design. The study design was longitudinal and observational. Subjects visited the University of Alabama at Birmingham for testing annually, at approximately the same time each year. Recruitment began in 1995 and continued until enough subjects were recruited. Thus, not all subjects joined the study during the same year; likewise, not all subjects completed all possible visits. Insulin sensitivity testing was incorporated into the protocol in 1996. Data used for the present study are from 1996 through 2001.

Protocol. Subjects were admitted into the General Clinical Research Center for an overnight stay during which S_I, fasting insulin, and AIR_g were obtained during a tolbutamide-modified, frequently sampled intravenous glucose tolerance test, as previously described (6). S_I was derived from minimal model analysis; AIR_g was calculated as the incremental area under the curve for insulin during the first 10 min after glucose injection; and fasting insulin was determined as the average insulin concentration in three baseline (pre–glucose injection) blood draws. Total body fat was determined by dual-energy X-ray absorptiometry (Lunar DPX-L, software version 1.5e; Lunar Radiation Corp., Madison, WI); body composition was not available on two boys at Tanner stage I, one girl at Tanner stage II, and one boy at Tanner stage V. Socioeconomic status (SES) was measured with the Hollingshead four-factor index of social class (11), which combines the educational attainment and occupational prestige for the number of working parents in the child's family. Scores ranged from 8 to 66, with the higher score indicating higher theoretical social status. SES information was not available on one subject. Tanner stage was determined through physical examination by a pediatrician. Stage I denotes prepubertal status, whereas stage V denotes young adult status; stages II–IV denote stages of pubertal transition. Total body fat and Tanner stage were included in all statistical models for S_I because both have been shown to influence this outcome measure in this cohort (6,12).

Determination of genetic admixture. Genotyping was performed at Pennsylvania State University. Molecular techniques used for the genotyping include the melting curve analysis of single nucleotide polymorphisms (McSNP) method described by Akey et al. (13) and agarose gel electrophoresis. Markers and techniques used for the identification of the ancestry-informative DNA sequences have previously been described by Parra et al. (8) and are available through dbSNP (http://www.ncbi.nlm.nih.gov/SNP/) using the handle PSA-ANTH. Markers used for this study, their chromosomal and centimorgan location, and their allelic difference between European and African parental populations are described in Table 1. All genotype information was translated into an individual value for ADM using a maximum likelihood method (14), where the likelihood that a particular multilocus genotype is from each of 100 different combinations of the two parental populations is calculated as the probability of the genotype given the allele frequencies in each parental population. The parental population combination where the specific multilocus genotype for an individual has the highest probability is thus the most likely and represents the ADM estimate for that person.

Statistical analyses. Because multiple phenotypic measures were available for each individual due to repeated, annual testing, a mixed linear model (PROC MIXED) was used to examine the relationship of ADM with S_I, fasting insulin, and AIR_g. To improve normality of the distribution of phenotypic variables, log transformations were used on total body fat, S_I, fasting insulin, and AIR_g for all statistical analyses; thus, all results shown were derived from log-transformed data. Tanner stage was modeled as a categorical variable in the statistical models, with Tanner = 5 as the reference value. Because some children remained at a given Tanner stage throughout several consecutive years of testing, an "age-nested-in-Tanner stage" component was included in the models. Although there was a high degree of colinearity between the Tanner stage and age variables, use of the nested term was necessary to account for changes in the dependent variables that occurred with age, within a given Tanner stage (12).

Exploratory analyses, including a quadratic and linear component of Tanner stage, and the interaction of these variables with ADM, were used to identify the most parsimonious model explaining variation in the dependent variables (data not shown). For S_I and fasting insulin, the model was defined by Tanner stage, age nested in Tanner stage, total fat, SES, and ADM. For AIR_g, the model was defined by Tanner stage, age nested in Tanner stage, S_I, SES, and ADM. Pearson correlation analysis was used to examine the association between ADM and SES. All statistical analyses were performed using SAS version 10.0 (SAS Institute, Cary, NC).

TABLE 1
Markers used for this study, their chromosomal and centimorgan location, and their allelic difference (frequency in population 1 minus frequency in population 2) between European and African parental populations.

Marker	Location	cM	African vs. European
MID 575	1p34.3	~64	0.130
MID 187	1p34.1	~75	0.370
FY-null	1q23.2	~165	0.999
AT3	1q25.1	~191	0.575
WI-11392	1q42.2	~252	0.444
WI-16857	2p16.1	~79	0.536
WI-11153	3p12.3	~106	0.652
GC*1F	4q13.3	79	0.697
GC*1S	4q13.3	79	0.538
SGC30055	5q23.1	~120	0.457
CYP3A4	7q22.1	~111	0.761
LPL	8p21.3	~39	0.479
D11S429	11q11	~70.9	0.429
DRD2-Taq I "D"	11q23.1	~105	0.535
APOA1	11q23.3	~113	0.505
GNB3	12p13.31	~15	0.463
OCA2	15q13.1	~16	0.631
MC1R314	16q24.3	~133	0.350
WI-14867	17p13.2	~10	0.448
WI-7423	17p12	~16	0.476
Sb19.3	19p13.11	~49	0.488
MID 154	20q11.22	~50	0.444

RESULTS

Descriptive statistics for the subjects by Tanner stage are shown in Table 2. Sample size is given for each combination of sex and Tanner stage and ranged from a high of 90 (boys, Tanner stage I) to a low of 7 (boys, Tanner stage V).

The distribution of African ADM was from 0 to 100%. Among children who identified themselves as European American, African ADM ranged from 0 to 21%, with the exception of one individual with a score of 61; among those who identified themselves as being African American, African ADM ranged from 50 to 100%. SES of the subjects ranged from 8 to 66. African admixture was significantly correlated with SES among African-American children ($r = -0.134$; $P < 0.05$) but not among Caucasian children ($r = -0.08$; $P = 0.220$).

In exploratory analyses for the dependent variable S_I, the quadratic term for Tanner stage was not significant. This result indicated that the decrease and subsequent rebound in S_I that occurs during puberty (15) was not

TABLE 2
Descriptive statistics by Tanner stage

Variable	Tanner I	Tanner II	Tanner III	Tanner IV	Tanner V
Boys					
n	90	52	19	10	7
Age (years)	9.3 ± 1.5	11.0 ± 1.3	12.0 ± 0.9	13.3 ± 1.0	14.1 ± 0.8
BMI (kg/m^2)	19.3 ± 3.6	23.2 ± 6.4	25.4 ± 5.8	24.6 ± 5.6	24.5 ± 4.2
Total fat (kg)	9.2 ± 6.7*	16.8 ± 12.1	21.4 ± 14.6	17.4 ± 14.6	16.7 ± 12.5†
S_I ($\times 10^{-5} \cdot min^{-1} \cdot pmol^{-1} \cdot l^{-1}$)	11.8 ± 6.3	7.7 ± 5.7	5.3 ± 3.2	7.2 ± 5.7	8.5 ± 7.8
Fasting insulin (pmol/l)	67.2 ± 34.2	87.0 ± 48.0	106.8 ± 63.0	80.4 ± 16.8	59.4 ± 28.8
AIR_g (pmol/l × 10 min)	6,174 ± 7,176	9,780 ± 8,460	16,050 ± 23,466	10,944 ± 12,324	7,314 ± 5,202
Girls					
n	73	67	62	30	18
Age (years)	9.2 ± 1.6	10.9 ± 1.3	12.3 ± 1.11	13.5 ± 1.1	14.3 ± 1.0
BMI (kg/m^2)	19.0 ± 4.7	21.7 ± 5.8	22.0 ± 4.7	23.4 ± 5.6	25.5 ± 6.1
Total fat (kg)	10.1 ± 7.6	15.2 ± 10.9‡	16.8 ± 10.1	20.2 ± 11.0	23.9 ± 11.9
S_I ($\times 10^{-5} \cdot min^{-1} \cdot pmol^{-1} \cdot l^{-1}$)	10.5 ± 7.2	7.5 ± 5.5	6.3 ± 4.5	6.8 ± 3.8	5.8 ± 3.5
Fasting insulin (pmol/l)	70.2 ± 40.2	97.2 ± 45.0	97.2 ± 52.8	88.2 ± 44.4	81.0 ± 33.6
AIR_g (pmol/l × 10 min)	6,288 ± 4,524	6,948 ± 4,746	6,612 ± 4,908	7,110 ± 3,510	5,514 ± 3,132

*n = 88; †n = 6; ‡n = 66.

statistically detectable in these data, perhaps due to the relatively small number of subjects at Tanner stages IV and V. Thus, only the linear component of Tanner stage was used in subsequent models. The independent effect of sex also was examined in exploratory analysis. Because sex was not significant in the model for S_I (P = 0.126), AIR_g (P = 0.365), or fasting insulin (P = 0.339; data not shown), it was not evaluated in the analyses.

Table 3 shows the results of the statistical model with S_I as the dependent variable, as predicted by Tanner stage, age nested in Tanner stage, total fat, SES, and ADM. ADM was independently related to S_I ($P < 0.001$). SES was not uniquely related to S_I (P = 0.052).

Table 4 shows the results of the model for fasting insulin, as predicted by Tanner stage, age nested in Tanner stage, total fat, SES, and ADM. ADM was independently related to fasting insulin ($P < 0.01$); SES was not (P = 0.074).

Table 5 shows the results of the model for AIR_g, where Tanner stage, age nested in Tanner stage, S_I, SES, and ADM were used as predicting variables. Both ADM ($P < 0.001$) and SES ($P < 0.05$) were uniquely related to AIR_g.

In the models for both S_I and AIR_g, the overall effect of Tanner stage was not significant, but the overall effect of age nested in Tanner stage was significant ($P < 0.05$).

DISCUSSION

The results of this study demonstrated that ADM explained a significant portion of the variance in S_I, fasting insulin, and AIR_g, whereas SES was independently related to AIR_g. These observations suggest that use of ADM can replace assignment of individuals to categorical racial groups; that lower S_I and higher fasting insulin among African Americans compared with European Americans may have a genetic basis; and that higher AIR_g among African Americans may be due to both genetic and environmental factors.

As reported in cross-sectional observations (6), body fat was a primary determinant of S_I, with more obese individuals having lower S_I. In contrast to reports from cross-sectional studies (12), Tanner stage was not independently related to S_I. This discrepancy may relate to the relatively small number of subjects available at the higher Tanner stages, and to the high correlation between Tanner stage

TABLE 3
Parameter estimates for mixed model with the dependent variable S_I

Effect	Estimate	SE	*P*
Intercept	5.4065	1.5183	0.0005
Tanner I	1.1113	1.4108	0.4322
Tanner II	1.5288	1.4353	0.2886
Tanner III	0.6601	1.4854	0.6574
Tanner IV	1.0127	1.6365	0.5370
Tanner V	0	—	—
Age(Tanner) I	0.09295	0.02596	0.0004
Age(Tanner) II	0.03337	0.03621	0.3576
Age(Tanner) III	0.09830	0.04727	0.0385
Age(Tanner) IV	0.08261	0.06902	0.2323
Age(Tanner) V	0.1458	0.09770	0.1367
Total fat	−0.5723	0.05487	<0.0001
African ADM	−0.00762	0.001292	<0.001
SES	−0.00723	0.003694	0.0525

TABLE 4
Parameter estimates for mixed model with the dependent variable fasting insulin

Effect	Estimate	SE	*P*
Intercept	−0.09500	1.2176	0.9379
Tanner I	−0.6287	1.1730	0.5928
Tanner II	−0.8173	1.1929	0.4944
Tanner III	−0.2747	1.2412	0.8252
Tanner IV	−0.05419	1.3682	0.9685
Tanner V	0	—	—
Age(Tanner) I	−0.05972	0.01998	0.0030
Age(Tanner) II	−0.02531	0.02732	0.3551
Age(Tanner) III	−0.06882	0.03878	0.0771
Age(Tanner) IV	−0.08737	0.05677	0.1249
Age(Tanner) V	−0.1004	0.08142	0.2184
Total fat	0.3769	0.03340	<0.001
African ADM	0.002211	0.000747	0.0037
SES	0.003764	0.002090	0.0743

TABLE 5
Parameter estimates for mixed model with the dependent variable AIR_g

Effect	Estimate	SE	*P*
Intercept	8.1235	1.1355	<0.0001
Tanner I	−0.1827	1.1234	0.8710
Tanner II	−0.1134	1.1455	0.9213
Tanner III	0.8785	1.1804	0.4580
Tanner IV	0.07426	1.3024	0.9546
Tanner V	0	—	—
Age(Tanner) I	−0.04863	0.01951	0.0132
Age(Tanner) II	−0.05602	0.02918	0.0559
Age(Tanner) III	−0.1417	0.03795	0.0002
Age(Tanner) IV	−0.06465	0.05554	0.2453
Age(Tanner) V	−0.07767	0.07811	0.3209
S_I	−0.3913	0.03792	<0.0001
African ADM	0.006891	0.001377	<0.0001
SES	−0.00817	0.003848	0.0358

and age. However, age nested within Tanner stage was significantly related to S_I, indicating that within Tanner stages I and III, S_I increased with age (12). Likewise, age nested within Tanner stage was uniquely and inversely related to AIR_g at Tanner stages I through III, perhaps reflecting an age-related decrease in β-cell function (12). The lack of significance of age nested within Tanner stage at Tanner stages IV and V may have been due to the relatively low sample size in these groups, or to the collinearity between Tanner stage and age; further study in children of higher pubertal stages will be needed to clarify this issue.

The model for AIR_g contained S_I as an independent variable. Thus, variables in the AIR_g model that emerged as significant reflect a contribution to AIR_g that is in addition to compensatory pancreatic phenomena (16). It has previously been reported that, at least in children, the disproportionately greater AIR_g among African Americans results from a combination of greater first-phase insulin secretion and lower hepatic insulin extraction (4). In the present study, the significant contribution of genetic admixture to AIR_g, independent of S_I and SES, suggests that genetic factors may influence pancreatic function, the ability of the liver to clear insulin, or both. Furthermore, results indicated that individuals with lower SES had relatively higher AIR_g, independent of S_I. Neither dietary factors (17) nor physical activity (18), both of which are highly associated with measures of SES, explained racial differences in AIR_g in cross-sectional analyses of this cohort during the subjects' prepubertal and early pubertal years. However, due to the limitations of lifestyle measures obtained by questionnaire, the possible contribution of diet and physical activity, as well as other components of SES, to AIR_g remains an open question.

In the model for fasting insulin, as in that for S_I, ADM explained a unique portion of the variance. This result could reflect the well-documented inverse association between S_I and fasting insulin (16). Age nested in Tanner stage showed a significant inverse relationship at Tanner stage I, indicating that fasting insulin declined with age in prepubertal children. This observation agrees with the observed increase in S_I with age during Tanner stage I (Table 3).

Limitations of this study include the small number of individuals with African ADM in the central range of the distribution; the small number of children at Tanner stages IV and V; and the use of ~20 molecular markers to characterize ADM. Use of additional markers, when available, will likely improve the genetic characterization of individuals, and increase the likelihood of successfully mapping genes associated with S_I or AIR_g.

In conclusion, results suggest that use of ADM can replace assignment of individuals to categorical racial groups. A further benefit of using ADM is the likelihood that, because it has more variability than a dichotomous race variable, it will explain more variance in S_I, AIR_g, and other physiological variables (19,20). The independent association of ADM with S_I and AIR_g indicated that lower S_I and higher AIR_g among African Americans may have a genetic basis. Higher AIR_g among African Americans may be due to social/environmental factors; identifying these factors will be an important step toward understanding and preventing racial and ethnic disparities in type 2 diabetes and cardiovascular disease.

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