

# Association of African Genetic Admixture with Resting Metabolic Rate and Obesity Among Women

José R. Fernández,<sup>\*‡</sup> Mark D. Shriver,<sup>‡‡</sup> T. Mark Beasley,<sup>‡</sup> Nashwa Rafla-Demetrious,<sup>§</sup> Esteban Parra,<sup>‡‡</sup> Jeanine Albu,<sup>§</sup> Barbara Nicklas,<sup>¶//</sup> Alice S. Ryan,<sup>//</sup> Paul M. McKeigue,<sup>\*\*</sup> Clive L. Hoggart,<sup>\*\*</sup> Roland L. Weinsier,<sup>\*†</sup> and David B. Allison<sup>\*‡</sup>

## Abstract

FERNÁNDEZ, JOSÉ R., MARK D. SHRIVER, T. MARK BEASLEY, NASHWA RAFLA-DEMETRIOUS, ESTEBAN PARRA, JEANINE ALBU, BARBARA NICKLAS, ALICE S. RYAN, PAUL M. MCKEIGUE, CLIVE L. HOGGART, ROLAND L. WEINSIER, AND DAVID B. ALLISON. Association of African genetic admixture with resting metabolic rate and obesity among women. *Obes Res.* 2003;11:904–911.

**Objective:** To investigate the role of genetic admixture in explaining phenotypic variation in obesity-related traits in a sample of African-American women ( $n = 145$ ) and to determine significant associations between obesity traits and admixture genetic markers.

**Research Methods and Procedures:** Associations between genetic admixture and BMI, resting metabolic rate, fat mass, fat-free mass, and bone mineral density were tested using linear regression considering the estimation of admixture by 1) a maximum-likelihood approach (MLA) and 2) a Bayesian analysis.

**Results:** Both the conservative MLA and the Bayesian

approach support an association between African genetic admixture and BMI. Evidence for the associations of African genetic admixture with fat mass and fat-free mass was supported by the Bayesian analysis; the MLA supported an association with bone mineral density. When the individual ancestry informative markers that were used to estimate admixture were tested for associations with BMI, significant associations were identified in chromosomes 1, 11, and 12.

**Discussion:** These results provide evidence supporting the application of admixture mapping methods to the identification of genes that result in higher levels of obesity among African-American women. Further research is needed to replicate and further explore these findings.

**Key words:** genetics, African Americans, resting metabolic rate, admixture, ancestry informative markers

## Introduction

Although health disparities among races and ethnic groups have been declared a priority for public health initiatives, the extent to which genetic and environmental factors account for ethnic and racial differences in complex traits such as obesity, cardiovascular disease, and diabetes continues to be enigmatic. Efforts to identify genetic variations accounting for group differences in such complex polygenic phenotypes continue to challenge researchers.

Most of the ethnic groups in the United States have resulted mainly from the intermixing of European, African, and Native-American populations during the colonization and continued habitation of the New World. Genetic variants or alleles from these previously isolated parental populations were brought together in new combinations establishing the gene pools of the various contemporary European-, African-, Hispanic-, and Native-American resident populations. Consequently, individuals of these popu-

Received for review October 16, 2002.

Accepted in final form May 19, 2003.

\*Department of Nutrition Sciences and the Clinical Nutrition Research Center and ‡Department of Biostatistics, Section on Statistical Genetics, The University of Alabama at Birmingham, Birmingham, Alabama; ‡‡Department of Anthropology, The Pennsylvania State University, University Park, Pennsylvania; §Obesity Research Center, St. Luke's/Roosevelt Hospital, Institute of Human Nutrition, Columbia University College of Physicians & Surgeons, New York, New York; ¶Section on Gerontology and Geriatric Medicine and Center for Human Genomics, Wake Forest University School of Medicine, Winston-Salem, North Carolina; //Department of Medicine, Division of Gerontology at The University of Maryland School of Medicine and The Geriatric Research Educational Clinical Center, Baltimore VA Medical Center, Baltimore, Maryland; \*\*Epidemiology Unit, London School of Hygiene and Tropical Medicine, London, United Kingdom.

†Deceased.

Address correspondence to Dr. José R. Fernández, Department of Nutrition Sciences, Division of Physiology and Metabolism, The University of Alabama at Birmingham, 1530 3rd Avenue S., Birmingham, AL 35294-3360.

E-mail: jose@uab.edu

Copyright © 2003 NAASO

lations, who inherit variants that predispose them either to disease-related traits or to a greater sensitivity to environmental exposure, will have a greater chance of acquiring the disease.

Epidemiological evidence has supported differences among individuals of various backgrounds in different obesity-related traits, including BMI and resting metabolic rate (RMR),<sup>1</sup> particularly when African-American women are compared with European-American women. For example, obesity is more prevalent in African-American women than their white counterparts, even after controlling for socioeconomic status (SES) (1). In addition, there are reports of lower levels of energy expenditure in African-American women (2–5). Higher bone mineral density (BMD) in African-American individuals when compared with European Americans has also been reported (6,7). Because these differences might result, in part, from the inheritance of disease-predisposing alleles from parental populations, the identification of such alleles may be a valuable tool for exploring the genetic component contributing to these health disparities. The estimation of the degree of parental admixture on members of genetically admixed populations has been described in the literature as an approach to identifying genetic influences of this sort (8–10). This approach has been used by Williams et al. (11) to suggest a genetic susceptibility for both diabetes and obesity by the negative association between European admixture and prevalence for type 2 diabetes and obesity in Pima Indians.

This study capitalizes on the estimation of the degree of individual genetic admixture to identify genetic influences in obesity-related traits using a specially selected panel of ancestry informative markers (AIMs). Associations between individual estimates of genetic admixture with measures of body composition, bone density, and RMR are tested in a sample of African-American women. Additionally, these AIMs are tested for an association with these phenotypes.

## Research Methods and Procedures

### Subjects

A total of 145 African-American women participated in this study. Participants were recruited at three different sites within the United States: Birmingham, Alabama ( $n = 46$ ), Baltimore, Maryland ( $n = 38$ ), and Manhattan, New York ( $n = 61$ ). Only individuals for whom a quantitative value for African genetic admixture (AFADM) was available were included in the analyses; however, some individuals had missing information of certain phenotypic variables.

Participation of subjects was in accordance with the regulations of the Institutional Review Board at each site.

### Body Composition

BMI was calculated from measured weight in kilograms divided by height in meters squared. Body composition measures of fat mass (FM), fat-free mass (FFM) and BMD were obtained by DXA (Model DPX-L; Lunar Radiation Corporation, Madison, WI) at each of the three sites.

### RMR

RMR was obtained by indirect calorimetry. This procedure consists of calculating energy expenditure and respiratory quotient from the uptake of oxygen and the production of carbon dioxide using the ventilated hood technique during a 30-minute period. The RMR protocol at each site has been provided elsewhere (3,12,13).

### SES

Because of the possible confounding effect of SES a crude measure of SES was obtained for 138 subjects by assigning the median SES according to the zip code of the subject's residential area at the time of the study. Information regarding the SES was obtained from the 1990 US Census (<http://www.facfinder.census.gov>).

### Genotyping

Genotyping was performed at The Pennsylvania State University using melting curve analysis of single-nucleotide polymorphisms (14) and agarose gel electrophoresis. Molecular techniques for the allelic identification of the markers have been described elsewhere (15,16). All markers sequences, experimental details, and parental population allele frequencies have been submitted to dbSNP database (<http://www.ncbi.nlm.nih.gov/SNP>) under the submitter identification handle PSU-ANTH.

Table 1 lists the markers used for the study, their chromosomal location and approximate distance in centimorgans (cM), and their  $\delta$  value for African and European parental populations, which refers to the difference in allelic frequencies between parental populations. Markers *WI-14867* and *CYP3A4* were not genotyped in the sample from Maryland; instead, *APOA1* and *Sb19.3* were genotyped only in this sample. Thus, every individual in the entire sample was genotyped for a total of 18 markers.

### Statistical Methods

Two different methods were used in the analysis of the data collected: a maximum-likelihood approach (MLA), where individual estimates of genetic admixture were calculated by the method described by Hanis et al. (17), and a Bayesian approach (BA) (10). In the MLA, the associations between AFADM and the phenotypes were tested with a conservative parametric linear model, and normality was

<sup>1</sup> Nonstandard abbreviations: RMR, resting metabolic rate; SES, socioeconomic status; BMD, bone mineral density; AIM, ancestry informative marker; AFADM, African genetic admixture; FM, fat mass; FFM, fat-free mass; cM, centimorgan(s); MLA, maximum-likelihood approach; BA, Bayesian approach.

**Table 1.** Markers informative for estimating admixture between African and European populations for this study, their chromosomal and centimorgan location, and their allelic difference,  $\delta$  (frequency in population 1 minus frequency in population 2), between European and African parental populations (AF/EU)

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

improved in certain variables by the use of transformations. A log-transformation was applied to BMD and a square-root transformation to FFM. BMI was transformed to 1/BMI, a transformation previously used to improve linearity in statistical models for obesity-related research (2,18,19). References to FFM, BMD, and BMI as dependent variables hereafter indicate the transformations described. No transformation was necessary for FM or RMR.

Simple regression models, where each of the dependent measures was regressed on AFADM, were used to detect outliers, defined as observations for which the absolute value of the standardized residual exceeded 3.0. No outliers were detected in any of the phenotypic variables. A multiple regression model was used to test the unique effect of AFADM on the dependent variables BMD, BMI, FFM, FM, and RMR. The values of RMR were adjusted by FM and FFM. In each model, age, SES, and a set of two dummy codes for the three sites were used as covariates. Because SES was not a significant variable for any of these models,

it was eliminated from the covariates in the final analyses. All the analyses for this approach were performed using the linear regression option of SPSS (version 10; SPSS Inc., Chicago, IL).

In the BA (10), the genotypic data of all individuals in the sample were used simultaneously to estimate individual levels of admixture and regression parameters in a model evaluating the association of admixture with the obesity-related traits measured. The model allows for linkage between marker loci and allows observations with missing data to be included. For each trait, the Bayesian model includes two regression models: a least-squares regression of trait on age, SES, site (two indicator variables for Maryland and New York, using Alabama as the baseline category), and admixture; and a least-squares regression of SES on site and admixture. Through this approach, the program incorporates information about site and admixture when sampling the posterior distribution of SES in the seven individuals with missing values for income.

BMI (the only phenotype that showed significant association with AFADM in both MLA and BA) was used as a dependent variable in a regression model that tested for association with genotype for each marker locus, adjusting for age and site. In the MLA, the model was also adjusted by the maximum-likelihood estimate of individual admixture (calculated excluding the marker serving as the independent variable). In the BA, this adjustment was not necessary; a test for association of the trait with locus ancestry (scored as 0, 1, or 2 gene copies of ancestry) is a specific test for linkage with genes underlying the ethnic differences in the trait (20). Score tests for this association were constructed by averaging over the posterior distribution as described previously (10).

## Results

Table 2 demonstrates descriptive statistics for the site-specific admixture estimate, age, and body composition variables. No significant differences were observed in levels of African admixture among the three sites. However, age significantly differed among the three sites ( $F = 103.6, p < 0.0001$ ). When the mean values of the obesity-related phenotypes at each site were compared, significant differences were observed for BMI ( $F = 29.03, p < 0.001$ ), FM ( $F = 34.09, p < 0.001$ ), FFM ( $F = 9.41, p < 0.001$ ), and BMD ( $F = 4.46, p < 0.013$ ), as qualified by a one-way ANOVA. After adjusting by FM and FFM, levels of RMR were not significantly different among the three sites ( $F = 0.363, p < 0.696$ ). Even after adjusting these variables by age, the results remained the same: significant differences across study sites in the body composition variables and no significant differences in RMR.

$R^2$  and significance values resulting from the association between the obesity-related phenotypes and AFADM are reported in Table 3.  $R^2$  values indicated in the table refer to

**Table 2.** Descriptive statistics for subjects studied at each of three sites (data shown as means  $\pm$  SD)

Site	N*	Age	Admixture estimate	RMR	Body composition			
					BMI (kg/m <sup>2</sup> )	FM	FFM	BMD
Alabama	46	33.08 $\pm$ 5.53	82.72 $\pm$ 14.06	1317.72 $\pm$ 191.07	25.52 $\pm$ 3.41	26.81 $\pm$ 8.50	42.90 $\pm$ 4.19	1.20 $\pm$ 0.08
Maryland	38	56.32 $\pm$ 5.97	80.92 $\pm$ 12.90	1546.26 $\pm$ 213.65	34.71 $\pm$ 4.24	44.29 $\pm$ 9.19	48.11 $\pm$ 6.29	1.24 $\pm$ 0.09
New York	61	34.57 $\pm$ 10.80	82.79 $\pm$ 16.86	1446.61 $\pm$ 220.39	29.86 $\pm$ 6.47	33.23 $\pm$ 12.44	53.11 $\pm$ 19.14	1.24 $\pm$ 0.07
All	145	39.83 $\pm$ 12.86	82.28 $\pm$ 14.96	1432.23 $\pm$ 226.18	29.78 $\pm$ 6.16	34.32 $\pm$ 12.41	48.62 $\pm$ 13.69	1.23 $\pm$ 0.08

\* Total number of subjects (N) based on individuals with an estimate of AFADM.

the contribution of AFADM on the dependent variable after removing the contribution of covariates (i.e., “semi-partial”  $R^2$  values). Significant  $R^2$  values were obtained for BMI and BMD, whereas values for FM, FFM, and RMR (adjusted by FM and FFM) were of borderline significance.

Table 4 shows the independent associations of genetic markers with BMI. Four different markers were significantly associated with BMI at the 0.05 probability level. Results from the AFADM-adjusted models are also shown in Table 4. The results of the adjusted models remained significant even when the adjustment for the association was performed using a value of admixture that included all markers for the individual admixture estimate (data not shown).

Results of the association between admixture and the phenotypic measures using BA are demonstrated in Table 5. The posterior means and 95% credible intervals from BA are asymptotically equivalent (with large sample size and noninformative prior distributions) to maximum-likelihood estimates and 95% confidence intervals. A 95% credible interval that does not overlap 0 is, thus, asymptotically equivalent to a  $p$  value  $<0.05$ . The estimate of the mean of population African admixture was 83% (95% credible interval: 81 to 86), and there was no evidence that income was related to admixture or that it differed among sites. The Bayesian analysis supported associations of BMI, FM, and FFM with African admixture with 95% credible intervals that did not overlap zero. The results from the test for linkage in the model with genes underlying ethnic differences in BMI supported only two loci (*APOAI* and *GNB3*) with evidence for linkage significant at  $p < 0.05$ . Because the test at locus *APOAI* uses additional information from the adjacent locus *DRD2TAQD*, which is only 4 cM away, it is not surprising that both *DRD2* and *APOAI* show associations in the same direction.

## Discussion

Both the conservative MLA and the BA support an association between AFADM and BMI. Evidence for the associations of AFADM with FM and FFM is stronger with the BA, which makes fuller use of the data, than with the classical analysis; however, for BMD, the proximity of overlap to 0 in the BA makes it equivalent to a  $p$  value just  $>0.05$ . Nevertheless, the results of this investigation support the relevance of using AIMs in studying the genetics of complex traits in admixed populations and suggest that the differences in the prevalence of obesity-related phenotypes among African-American and European-American women could be partly attributable to genetic factors. These findings also provide insight into the role of genes accounting for racial differences in complex biomedical traits, suggesting a genetic contribution to the well-documented higher levels of BMI in African-American vs. European-American individuals.

**Table 3.** Results of the association between AFADM and the obesity-related phenotypes

Dependent variable	Slope	Lower CI	Upper CI	$R^2$ *	<i>p</i> value
BMI	-0.0000916	-0.0001583	-0.0000248	0.032	0.008
BMD	0.0003774	0.0000557	0.0006991	0.039	0.022
FFM	0.0099525	-0.0010960	-0.0210010	0.015	0.077
FM	0.1052679	-0.0169683	0.2275041	0.013	0.091
RMR	-1.7783775	-3.8555188	0.2987637	0.011	0.093

\*  $R^2$  values represent the amount of phenotypic variance accounted by AFADM, after removing the effect of covariates.

After establishing a significant association between AFADM and BMI, it was intuitively reasonable to expect similarly significant results with measures of FM and FFM in the MLA. Only close-to-significant results for both phenotypes were shown by MLA, most likely because of the small sample size, whereas the BA supported the expected associations with both FM and FFM. Using BA, we noted a significant association between AFADM and percentage of body fat, which was not supported by MLA (data not shown).

In the case of RMR, a small sample size might also have explained the lack of association between AFADM and RMR using the MLA. In the BA, the 95% posterior interval for the effect of admixture overlaps zero, but with a very wide range (up to 10 SDs), which might suggest that not enough information was available to fit a complex model with seven covariates. The association between AFADM and RMR was somewhat expected, based on evidence from epidemiological studies, wherein lower RMR levels have been found in African-American compared with other North-American, genetically admixed groups (3–5,13), and yet the slope of the relationship between RMR and body composition between African-American and African popu-

lations did not differ (21). Interestingly, on preliminary data analysis, a significant association between RMR and AFADM was observed in the New York sample, but not in the Maryland or Alabama samples (data not shown). This observation might provide insight into reported differences in energy levels according to geographic location (22). Future investigations relating the role of genetic admixture to RMR in large samples of admixed populations are warranted for enhancing understanding of this phenomenon.

Interpretations regarding the extent to which AFADM explains variation in each of the studied phenotypes deserves discussion. The  $R^2$  values presented in Table 3 represent biased estimates of the association of admixture with these phenotypes. In part, this is because of the lack of information that the value of AFADM provides to the model. AFADM ranged in the samples from 35 to 100; therefore, no information is available at lower levels of AFADM. Also, the  $R^2$  estimates depend on how much AFADM varies among individuals, and the MLA tends to underestimate the true relationship by not allowing for uncertainty in the individual admixture estimates. Finally, the sample was selected at some sites for extremes of BMI that can inflate the estimate of proportion of variance.

**Table 4.** Results of the associations of the independent markers and BMI using MLA

Phenotype	Marker	Location	<i>p</i> value	
			Nonadjusted*	Adjusted†
BMI	FY-Null	1q23.2	0.006	0.008
BMI	AT3	1q25.1	0.087	0.021
BMI	GNB3	12p13.31	0.009	0.025
BMI	DRD2TAQD	11q23.2	0.013	0.016

\* Nonadjusted refers to a statistical model where the estimate of the individual admixture considering all the markers was used as a covariate in the regression model.

† Adjusted refers to the statistical model where an estimated value for individual admixture calculated after excluding the marker serving as the independent variable was used as a covariate.

**Table 5.** Results from the Bayesian model

	Phenotypes														
	BMI (kg/m <sup>2</sup> )			BMD			FM			FFM			RMR*		
	Posterior mean	2.5%	97.5%	Posterior mean	2.5%	97.5%	Posterior mean	2.5%	97.5%	Posterior mean	2.5%	97.5%	Posterior mean	2.5%	97.5%
Intercept	29.7	28.8	30.5	1.23	1.21	1.24	33.3	31.7	35.5	45.9	44.9	47.0	1.42	1.31	1.55
Age	0.17	0.08	0.27	0.000	-0.011	0.011	0.37	0.15	0.58	0.03	-0.10	0.15	-0.05	-0.10	0.00
SES	-0.03	-0.11	0.05	0.000	-0.011	0.011	-0.06	-0.22	0.11	0.07	-0.02	0.17	0.006	-0.036	0.041
Maryland	5.4	2.4	8.5	0.044	-0.014	0.103	10.7	4.1	17.4	4.7	0.9	8.6	0.10	-0.01	0.22
New York	4.3	2.4	6.1	0.041	0.007	0.075	7.3	3.2	11.3	4.4	2.2	6.7	0.02	-0.06	0.09
Admixture	18.5	5.4	32.9	0.22	-0.01	0.51	36.9	-88.9	-1.4	24.2	6.5	47.7	-0.03	-0.56	1.59
Residual SD	4.6	4.0	5.2	0.080	0.064	0.096	9.6	8.3	11.0	5.3	4.5	6.2	0.16	0.13	0.19

\* For computational reasons in this analysis, RMR was divided by 1000, and age, income, FM, and FFM were standardized to have SD = 1. Results in RMR also included FM (posterior mean = 0.12; 2.5% = 0.08; 97.5% = 0.16) and FFM (posterior mean = 0.09; 2.5% = 0.04; 97.5% = 0.14).

Therefore, the percent variance explained is not necessarily a meaningful measure of strength of association in relation to observed ethnic difference. Nevertheless, the results of the study support the hypothesis that AFADM contributes to obesity traits in this population, characterizing the role of genetics in observed racial/ethnic differences in these phenotypes. Future research using representative samples will be needed to produce unbiased estimates of percent variance.

The genotype/phenotype associations described in the results support previously reported findings for obesity-related traits. The significant association in chromosome 1 for BMI occurred in a region close to the *LMNA* gene, which has been associated with BMI in other populations (23,24) and close to the locus at which Vionnet et al. (25) reported suggestive linkage to type 2 diabetes. Variants of the dopamine receptor in chromosome 11 (*DRD2TAQD*) have also been associated with weight and height (26) and BMI (27), and the *GNB3* allele has been associated with BMI in a number of populations (28,29). It is important to reiterate that the association tests in this study were performed using those AIMs, namely markers that have demonstrated differences in parental frequencies, which were available to the investigators. Although some of these AIMs may be nonfunctional polymorphisms, the use of these markers is appropriate because their association with the phenotype allows the identification of chromosomal regions influencing the trait. Given the limited amount of markers in the panel tested in this study, only limited regions of the genome were scanned. There are other regions across the genome influencing obesity-related traits that were not tested in this study because the regions were not defined in our battery of markers.

In the MLA, several markers showed significant association with BMI, even after adjustment for admixture. The strongest association of a marker with BMI was with *FY-Null*, which is almost perfectly informative for ancestry because the null allele is almost fixed in West-African populations and very rare in non-Africans. A limitation of the MLA is that it relies on “plugging in” the maximum-likelihood estimates of admixture into a regression model that does not allow for the uncertainty in these measurements. Thus, associations of the trait with marker loci may persist after adjustment for admixture because of residual confounding. In the BA, this uncertainty is correctly accounted for by using a score test that averages over the posterior distribution of admixture. However, the fact that other associations with obesity-related traits have been reported with regard to this region does not rule out the possible involvement of the chromosomal region in explaining ethnic and racial differences in obesity-related traits and deserves further research.

Several other limiting aspects of the study deserve further discussion. Although this investigation reports interesting

results, it is limited by a relatively small sample size and the limited number of AIMs. The study did not measure any cultural or environmental component that might influence the phenotypes, and the proxy measure of SES, although not significant in any of the model, was fairly crude and might not necessarily reflect the SES of the subjects at the time of participation in the study. The strength of environmental effects on obesity is apparent from the large differences in mean BMI among the three study sites, which were not explained by differences in admixture. Without more detailed measurements of social, economic, and behavioral factors related to obesity, we cannot rule out confounding by environmental factors as a possible explanation for the observed relationship with admixture. Also, the design and size of the study did not allow for the consideration of models testing for possible interactions that might have contributed to phenotypic variability.

This study supports the use of admixture mapping as a tool to identify genetic influences in obesity traits, as previously proposed by Williams et al. (11). Further research is needed with this approach, including the identification of more markers, the consideration of other admixed populations, such as Afro-Caribbeans, the inclusion of environmental measures, and the use of larger samples.

### Acknowledgments

We thank the volunteers in New York, Alabama, and Maryland, who gave their time and DNA for this research. This work was supported, in part, by the following: National Institute of Diabetes and Digestive and Kidney Diseases Grant DK53958 and National Human Genome Research Institute Grant HG02154 (to M. D. S.); NIH Grants IR01MH60343-01A1 (to P. M. M.), P30DK056336, R01ES09912, and R01DK056366; and a grant from the Knoll Pharmaceutical Company Weight Risk Investigators Study Council Program (to D. B. A.).

### References

1. **Allison DB, Edlen-Nezin L, Clay-Williams G.** Obesity among African American women: prevalence, consequences, causes, and developing research. *Womens Health*. 1997;3:243–74.
2. **Gallagher D, Heymsfield SB, Heo M, Jebb SA, Murgatroyd PR, Sakamoto Y.** Healthy percentage body fat ranges: an approach for developing guidelines based on body mass index. *Am. J Clin Nutr*. 2000;72:694–701.
3. **Nicklas BJ, Berman DM, Davis DC, Dobrovolsky CL, Dennis KE.** Racial differences in metabolic predictors of obesity among postmenopausal women. *Obes Res*. 1999;7:463–8.
4. **Hunter GR, Weinsier RL, Darnell BE, Zuckerman PA, Goran MI.** Racial differences in energy expenditure and aerobic fitness in premenopausal women. *Am. J Clin Nutr*. 2000;71:500–6.
5. **Lovejoy JC, Champagne CM, Smith SR, de Jonge L, Xie H.** Ethnic differences in dietary intakes, physical activity, and energy expenditure in middle-aged, premenopausal women: the Healthy Transitions Study. *Am. J Clin Nutr*. 2001;74:90–5.
6. **Wright NM, Papadea N, Veldhuis JD, Bell NH.** Growth hormone secretion and bone mineral density in prepubertal black and white boys. *Calcif Tissue Int*. 2002;70:146–52.
7. **Wagner DR, Heyward VH.** Measures of body composition in blacks and whites: a comparative review. *Am. J Clin Nutr*. 2000;71:1392–402.
8. **Shriver MD, Smith MW, Jin L, et al.** Ethnic-affiliation estimation by use of population-specific DNA markers. *Am. J Hum Genet*. 1997;60:957–64.
9. **McKeigue PM.** Mapping genes underlying ethnic differences in disease risk by linkage disequilibrium in recently admixed populations. *Am. J Hum Genet*. 1997;60:188–96.
10. **McKeigue PM, Carpenter JR, Parra EJ, Shriver MD.** Estimation of admixture and detection of linkage in admixed populations by a Bayesian approach: application to African-American populations. *Ann. Hum Genet*. 2000;64:171–86.
11. **Williams RC, Long JC, Hanson RL, Sievers ML, Knowler WC.** Individual estimates of European genetic admixture associated with lower body-mass index, plasma glucose, and prevalence of type 2 diabetes in Pima Indians. *Am. J Hum Genet*. 2000;66:527–38.
12. **Weinsier RL, Hunter GR, Desmond RA, Byrne NM, Zuckerman PA, Darnell BE.** Free-living activity energy expenditure in women successful and unsuccessful at maintaining a normal body weight. *Am. J Clin Nutr*. 2002;75:499–504.
13. **Albu J, Shur M, Curi M, Murphy L, Heymsfield SB, Pi-Sunyer FX.** Resting metabolic rate in obese, premenopausal black women. *Am. J Clin Nutr*. 1997;66:531–8.
14. **Akey JM, Sosnoski D, Parra E, et al.** Melting curve analysis of SNPs (McSNP): a gel-free and inexpensive approach for SNP genotyping. *Biotechniques*. 2001;30:358–67.
15. **Parra EJ, Kittles RA, Argyropoulos G, et al.** Ancestral proportions and admixture dynamics in geographically defined African Americans living in South Carolina. *Am. J Phys Anthropol*. 2001;114:18–29.
16. **Shriver MD, Parra EJ, Dios S, et al.** Skin pigmentation, biogeographical ancestry and admixture mapping. *Hum Genet*. 2003;112:387–99.
17. **Hanis CL, Chakraborty R, Ferrell RE, Schull WJ.** Individual admixture estimates: disease associations and individual risk of diabetes and gallbladder disease among Mexican-Americans in Starr County, Texas. *Am J Phys Anthropol*. 1986;70:433–41.
18. **Flegal KM.** Is an inverted weight-height index a better index of body fatness? *Obes Res*. 1997;5:93S (abstr).
19. **Fernandez JR, Heo M, Heymsfield SB, et al.** Is percentage body fat differentially related to body mass index in Hispanic Americans, African Americans, and European Americans? *Am. J Clin Nutr*. 2003;77:71–5.
20. **McKeigue PM.** Mapping genes that underlie ethnic differences in disease risk: methods for detecting linkage in admixed populations, by conditioning on parental admixture. *Am. J Hum Genet*. 1998;63:241–51.
21. **Luke A, Rotimi CN, Adeyemo AA, et al.** Comparability of resting energy expenditure in Nigerians and U. S. blacks. *Obes Res*. 2000;8:351–9.

22. **Goran MI, Nagy TR, Gower BA, et al.** Influence of sex, seasonality, ethnicity, and geographic location on the components of total energy expenditure in young children: implications for energy requirements. *Am J Clin Nutr.* 1998;68:675–82.
23. **Hegele RA, Cao H, Harris SB, Zinman B, Hanley AJ, Anderson CM.** Genetic variation in LMNA modulates plasma leptin and indices of obesity in aboriginal Canadians. *Physiol Genomics.* 2000;3:39–44.
24. **Hegele RA, Cao H, Huff MW, Anderson CM.** LMNA R482Q mutation in partial lipodystrophy associated with reduced plasma leptin concentration. *J Clin Endocrinol Metab.* 2000;85:3089–93.
25. **Vionnet N, Hani E, Dupont S, et al.** Genomewide search for type 2 diabetes-susceptibility genes in French whites: evidence for a novel susceptibility locus for early-onset diabetes on chromosome 3q27-qter and independent replication of a type 2-diabetes locus on chromosome 1q21–q24. *Am J Hum Genet.* 2000;67:1470–80.
26. **Comings DE, Flanagan SD, Dietz G, Muhleman D, Knell E, Gysin R.** The dopamine D2 receptor (DRD2) as a major gene in obesity and height. *Biochem Med Metab Biol.* 1993;50:176–85.
27. **Spitz MR, Detry MA, Pillow P, et al.** Variant alleles of the D2 dopamine receptor gene and obesity. *Nutr Res.* 2000;20:371–80.
28. **Hegele RA, Anderson C, Young TK, Connelly PW.** G-protein beta3 subunit gene splice variant and body fat distribution in Nunavut Inuit. *Genome Res.* 1999;9:972–7.
29. **Siffert W, Forster P, Jockel KH, et al.** Worldwide ethnic distribution of the G protein beta3 subunit 825T allele and its association with obesity in Caucasian, Chinese, and Black African individuals. *J Am Soc Nephrol.* 1999;10:1921–30.