nature publishing group

Admixture Mapping of Quantitative Trait Loci for BMI in African Americans: Evidence for Loci on Chromosomes 3q, 5q, and 15q

Analabha Basu[1], Hua Tang[2], Donna Arnett[3], C. Charles Gu[4], Tom Mosley[5], Sharon Kardia[6], Amy Luke[7], Bamidele Tayo[7], Richard Cooper[7], Xiaofeng Zhu[8] and Neil Risch[1,9,10]

Obesity is a heritable trait and a major risk factor for highly prevalent common diseases such as hypertension and type 2 diabetes. Previously we showed that BMI was positively correlated with African ancestry among the African Americans (AAs) in the US National Heart, Lung, and Blood Institute's Family Blood Pressure Program (FBPP). In a set of 1,344 unrelated AAs, using Individual Ancestry (IA) estimates at 284 marker locations across the genome, we now present a quantitative admixture mapping analysis of BMI. We used a set of unrelated individuals from Nigeria to represent the African ancestral population and the European American (EA) in the FBPP as the European ancestral population. The analysis was based on a common set of 284 microsatellite markers genotyped in all three groups. We considered the quantitative trait, BMI, as the response variable in a regression analysis with the marker location specific excess European ancestry as the explanatory variable. After suitably adjusting for different covariates such as sex, age, and network, we found strong evidence for a positive association with European ancestry at chromosome locations 3q29 and 5q14 and a negative association on chromosome 15q26. To our knowledge, this is the largest quantitative admixture mapping effort in terms of sample size and marker locus involvement for the trait. These results suggest that these regions may harbor genes influencing BMI in the AA population.

Obesity (2009) **17,** 1226–1231. doi:10.1038/oby.2009.24

INTRODUCTION

Although obesity is an individual clinical condition, it is increasingly viewed as a serious and growing worldwide public health problem. Obesity is believed to predispose to all the major killer diseases such as type 2 diabetes, cardiac disorders, hypertension, stroke, metabolic diseases, and even some forms of cancer (1). The prevalence of obesity has been continually rising for two decades (2). A common and inexpensive surrogate to measure obesity is BMI, defined as the ratio of weight in kilograms to squared height in meters. The variable BMI has its limitations, as it may be differentially affected by lean mass and bone content, which vary among population groups. However, an advantage of analyzing BMI is that it is a continuously measured trait, which generally provides greater power in searching for explanatory covariates than overweight or obesity defined by arbitrary cutoffs.

Though it is largely believed that excessive energy intake and a sedentary lifestyle of the developed world has been the major cause behind the obesity epidemic (3), other factors including genetic predisposition are also deemed responsible. Genetic factors contribute significantly to obesity (4), with heritability estimates of BMI ranging from 30 to 70% (4,5). In the present sample, estimated heritability, calculated for the three different networks, ranged between 45 and 62% (6,7). There have been numerous efforts to identify genes and chromosomal regions responsible for BMI, using genome-wide linkage and association analysis (5). Although a number of genes with rare mutations are known to lead to increased BMI and obesity, such as the melanocortin 4 receptor gene (8), most recently convincing evidence for the role of a common polymorphism in the *FTO* and *PCSK1* gene with a modest effect on BMI has been presented (9,10).

New world admixed populations provide unique opportunities for genetic admixture mapping studies (11–13). The African American (AA) population of the United States is typically represented by admixture of European and African ancestral genomes in different proportions with some spatial

[1]Institute for Human Genetics, University of California, San Francisco, California, USA; [2]Department of Genetics, Stanford University, Stanford, California, USA; [3]Department of Epidemiology, School of Public Health, University of Alabama, Birmingham, Alabama, USA; [4]Division of Biostatistics, Washington University School of Medicine, St Louis, Missouri, USA; [5]Department of Epidemiology, University of Mississippi Medical Center, Jackson, Mississippi, USA; [6]Department of Epidemiology, School of Public Health, University of Michigan, Ann Arbor, Michigan, USA; [7]Department of Preventive Medicine & Epidemiology, Loyola University, Maywood, Illinois,USA; [8]Department of Epidemiology and Biostatistics, Case Western Reserve University School of Medicine, Cleveland, Ohio, USA; [9]Department of Epidemiology and Biostatistics, University of California, San Francisco, California, USA; [10]Division of Research, Kaiser Permanente, Oakland, California, USA.
Correspondence: Neil Risch (rischn@humgen.ucsf.edu)

Received 20 August 2008; accepted 13 January 2009; published online 19 February 2009. doi:10.1038/oby.2009.24

variation (14–16). Several studies have examined the correlation between European (or African) ancestry in AAs and BMI or obesity (17–19). Three previous studies have demonstrated a positive association between African ancestry and BMI (17), a positive association of European ancestry with obesity-related traits (16), and no correlation of ancestry with BMI (19). In a prior analysis of the AA participants in the Family Blood Pressure Program (FBPP) (20), we found a positive correlation between BMI and individual African ancestry estimated from genome-wide microsatellite markers (16). In this study, we now present results of an analysis examining the correlation of BMI with estimated ancestry proportions at each of 284 marker loci among 1,344 unrelated AA subjects from the same FBPP population, in a search for potential locus-specific effects.

METHODS AND PROCEDURES

Subjects

The FBPP is a large multicenter genetic study of high blood pressure and related conditions in multiple racial/ethnic groups, including European Americans (EAs), AAs, Mexican Americans, Asians, and Asian Americans (20). It includes four component networks: GenNet, GENOA, HyperGEN, and SAPPHIRE. GenNet, GENOA, and HyperGEN independently collected samples from EA and AA families. GenNet sampled AA and EA nuclear families in Maywood, Illinois and Tecumseh, Michigan, respectively, through identification of a young middle-aged proband with elevated blood pressure. GENOA sampled AA sibships containing sibling pairs with hypertension from Jackson, Mississippi and EA sibships with an affected proband from Rochester, Minnesota. HyperGEN recruited AA and EA hypertensive siblings and random unrelated individuals from five field centers (AA from Birmingham, Alabama and Forsyth County, North Carolina; EA from Salt Lake City, Utah, Minneapolis, Minnesota, Framingham, Massachusetts, and Forsyth County, North Carolina). All individuals who participated in the FBPP gave informed consent; the Institutional Review Board at each clinic site approved all protocols, and a Certificate of Confidentiality was obtained from the Federal Government for this study.

All the individuals we included in the study were unrelated AA from field centers of GenNet, GENOA, and HyperGEN. Race/ethnicity information was obtained by self-description. To maximize the number of unrelated individuals in our sample, whenever possible we selected unrelated founder individuals, otherwise one randomly selected individual per family. Our final sample of 1,344 individuals consisted of 280 individuals who were sampled by the GenNet network, 349 individuals sampled by the GENOA network, and 715 individuals sampled by the HyperGEN network.

Genotyping

DNA was extracted from whole blood by standard methods by each of the four FBPP networks and was sent to the US National Heart, Lung, and Blood Institute's Mammalian genotyping service in Marshfield, Wisconsin, for genotyping. Screening set 8 (372 highly polymorphic microsatellite markers with an average map distance of 10 cM) was used for all four networks.

Statistical analysis

We used the computer program STRUCTURE (21,22) to estimate genome-wide, as well as site-specific ancestries in all AA participants. The linkage model was used, with genetic distance between markers specified according to the Marshfield map. In each analysis, the MCMC algorithm was run for 100,000 steps of burn-in followed by another 100,000 steps.

For the analysis of 1,344 FBPP AAs, we assumed a two-ancestral populations' model reflecting African and European ancestry. In these subjects, there was evidence of only very modest Native American ancestry (<1% on average), at best. We also included 1,378 unrelated non-Hispanic white participants from the FBPP as well as 127 African individuals from the Human Genome Diversity Project (23). This latter set of individuals had been genotyped at >300 short tandem repeats at the time of our analysis, and we included genotypes at 284 markers which were also genotyped in the FBPP individuals.

At each locus we calculated, for each individual, an ancestry deviation defined as the estimated ancestry at that location minus the background ancestry estimated from the genome-wide markers for that individual.

Specifically, let $q_k^{i,l}$ be the locus-specific ancestry of individual i ($i = 1, 2, \ldots, N$) at marker locus l ($l = 1, 2, \ldots, L$) estimated from STRUCTURE. We compute the overall (genome-wide) individual admixture $\left(\overline{q_k^i}\right)$ for the individual i as the average individual admixture per locus:

$$\overline{q_k^i} = \frac{\sum_{l=1}^{L} q_k^{i,l}}{L}$$

We computed the ancestry difference at each locus, using the genome-wide Individual Ancestry (IA) as baseline. Specifically for individual i, the ancestry difference for ancestral population k at marker l is defined as:

$$x_l^i = \left(q_k^{i,l} - \overline{q_k^i}\right)$$

Note that we have dropped the suffix k pertaining to the population from which the ancestry coefficients are derived. The variable x_l^i was then used as the primary independent variable in a linear regression model with BMI (transformed) as the dependent variable.

As we have only two ancestral populations, each individual's African (IA-AF) and European (IA-EU) ancestry sum to one. Therefore, IA-EU = [1 − (IA-AF)], and the same is true for the ancestry deviation at a particular location from an individual's genome-wide average ancestry. Thus, for any individual, the African and European ancestry deviations at a specific locus sum to one and are completely collinear in a regression analysis. Hence, only one term was included. Also, any regression result for European ancestry deviation is identical to a result using African ancestry deviation instead, with the sign of the regression coefficient in the opposite direction. Without loss of generality, we have used the excess European ancestry as our independent variable, and interpreted our findings based on that.

Age, sex, and network were also included as covariates in this analysis, if significant. Because of a highly significant sex effect, we also allowed for interaction between sex and network in the covariate adjustment. The standardized regression coefficient of x_l^i, defined as r_l^i, is distributed as asymptotically normal and was used to assess statistical significance.

To account for multiple testing (284 markers), we performed a permutation analysis in which we randomly reassigned the BMI and covariate data to individuals, whose genetic ancestry estimates for the 284 marker locations remained intact. This procedure preserved the correlation structure of the markers and the correlation structure of BMI and covariates, but dissociated the relationship between the markers and phenotypes. For each permuted data set, we performed the same regression analysis of BMI on excess ancestry at each marker location, as was done for the original data, and obtained the most extreme values (positive and negative) of r_l (the Z-score statistics). One thousand permutations were performed. To derive P values adjusted for multiple testing, we determined the percentage of times out of 1,000 permutations that an observed value of r_l was exceeded in the permuted data analysis.

Table 1 Demographics of study sample

	GenNet		GENOA		HyperGEN	
	Women	Men	Women	Men	Women	Men
Number of individuals	164	116	241	108	473	242
Average (BMI)	31.71 ± 8.6	27.38 ± 6.4	31.67 ± 7.3	29.37 ± 4.6	34.28 ± 8.3	29.34 ± 6.6
Average (age)	41.97 ± 12.6	40.75 ± 11.8	59.71 ± 9.8	60.85 ± 9.1	50.51 ± 12.6	50.83 ± 13.2
European ancestry (%)	13.48	13.87	14.86	14.76	12.53	13.06

Table 2 ANOVA results on log(log(BMI))

	df	Sum Sq	Mean Sq	*F* value	*P*
Age	1	0.0045	0.0045	1.0493	0.30585
Sex	1	0.4082	0.4082	95.0617	$<2.2 \times 10^{-16}$
Network	2	0.1116	0.0558	12.9926	2.579×10^{-6}
Sex × network	2	0.0336	0.0168	3.9140	0.02019
Residuals	1,337	5.7415	0.0043		

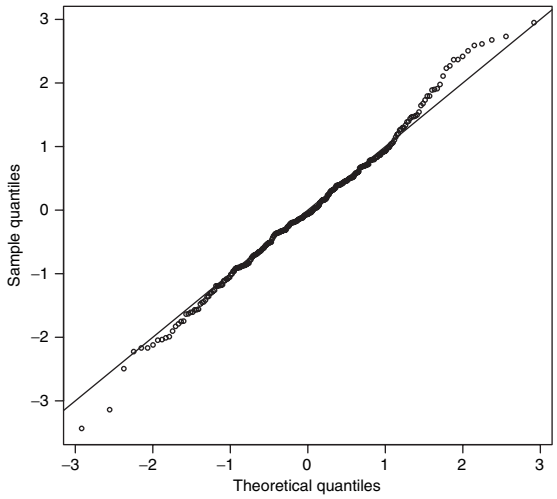

Figure 1 Q–Q plot comparing r_l with a standard normal distribution.

RESULTS

Sample demographics are given in **Table 1**. There were 878 women and 466 men. The subjects from the GenNet network were the youngest (average age 41) and subjects from GENOA the oldest (average age 60), while the HyperGen subjects were in between (average age 51). Average BMIs were generally higher in women than men, and there was little variation in BMI among networks. Average European ancestry varied modestly among the three networks, as was previously observed (16).

The distribution of BMI for the 1,344 unrelated individuals in this study was positively skewed. Neither the 1/BMI nor the $\log_e$(BMI) transformation, generally found in the literature, provided a satisfactory normalization of the data. However, a loglog transformation of BMI did make the distribution normal (**Supplementary Figure S1**). The trait LLBMI, which was defined as the loglog transformation of the original BMI, was strongly affected by sex and study center but not age (or age^2) when tested by ANOVA (**Table 2**).

After adjusting the LLBMI values for sex, study network, and the interaction between sex and network, we regressed it on excess European ancestry ($\boldsymbol{x}_l$) at each locus l (l = 1–284). The ratio (r_l) of the estimated slope of the regression (b_l) divided by its standard error (s_l) is asymptotically normal. We looked at regions with high absolute value of r_l. A positive value of the gradient b_l (and hence r_l) at the marker locus l implies that BMI is positively correlated with excess European ancestry (and negatively correlated with African ancestry) at that locus while a negative value of r_l implies that BMI is negatively correlated with European ancestry (and positively correlated with African ancestry) at that locus.

A Quantile–Quantile (Q–Q) plot of the r_l values against a normal distribution reveals that the fit is good except for the tails. There is a significant bulge in the right tail and at least two points in the left tail of the distribution also appear to be outliers (**Figure 1**). **Table 3** lists all markers for which the absolute value of the ratio r_l was >1.96 (corresponding to a two-sided unadjusted *P* value of 0.05). There are 11 points in the left tail and 13 in the right tail with absolute values >1.96, compared to 7 expected in each tail by chance. The three most extreme points in the left tail of the distribution are three consecutive markers, all from chromosome region 15q25.3–26.2. The next locus lying posterior to 15q26.2 at 15q26.3 (D15S642 or GATA27A03) also has a low r_l value of −2.12. The points that constitute the bulge in the right tail of the distribution are markers primarily from chromosome regions 3q28–29 and 5q14–23. There are also several points from the region 16p11.2–13.1.

To check the significance of our findings, we ran a permutation test in which we randomly assigned the phenotype and the related covariates to an individual's genotype, and regressed it on the locus specific excess European ancestry ($\boldsymbol{x}_l$) (see Methods). In 1,000 permutations, the minimum of 284 r_l scores only once crossed −3.14 and never crossed −3.43. The maximum also crossed 2.95 only once. Hence, the results associated with the markers D15S816, D15S652, and D3S1311 have empirical adjusted *P* values <0.002. We have done some additional analyses to show that these values are not due to "outlier" effects. Specifically, we looked at the scatter plot of individual excess European ancestry and LLBMI to search for outlier points with very high (or low) individual excess European ancestry at a locus coupled with a very high (or low) BMI value, which could distort the results. However, no such "outlier" points were identified (**Supplementary Figure S2**).

Table 3 Marker locations with the most significant regression on ancestry

DNAME	Location and distance (cM)	Estimated (b_l)	Estimated (r_l)	Marker names
Left Tail				
D15S816	15q26.2 (100.59)	−5.784	−3.433	GATA73F01
D15S652	15q26.1 (90.02)	−3.572	−3.139	ATA24A08
D15S655	15q25.3 (82.84)	−2.559	−2.493	ATA28G05
Unknown	1q32.2 (226.16)	−4.027	−2.225	GATA124F08
D1S235	1q42.3 (254.64)	−1.632	−2.168	AFM203YG9
D1S3462	1q42.2 (247.23)	−2.081	−2.167	ATA29C07
D15S642	15q26.3 (122.14)	−3.235	−2.120	GATA27A03
D4S1652	4q35.2 (208.07)	−2.236	−2.046	GATA5B02
D1S549	1q41 (239.66)	−2.423	−2.036	GATA4H09
D7S1818	7p12.3 (69.56)	−2.865	−2.008	GATA24D12
D7S817	7p14.3 (50.29)	−2.512	−1.990	GATA13G11
Right tail				
D5S1480	5q32 (147.49)	5.320	1.977	ATA23A10
D5S1501	5q14.1 (85.25)	2.438	2.109	GATA52A12
D16S769	16p12.1 (50.6)	2.756	2.233	GATA71H05
D16S753	16p11.2 (57.79)	3.135	2.270	GGAA3G05
D16S748	16p13.13 (22.65)	2.464	2.367	ATA3A07
D5S1725	5q14.3 (97.82)	1.555	2.369	GATA89G08
D16S764	16p13.11 (29.97)	2.815	2.418	GATA42E11
D5S1505	5q23.1 (129.83)	8.552	2.507	GATA62A04
D5S816	5q31.1–31.2 (139.33)	7.821	2.591	GATA2H09
D11S1984	11p15.5 (2.11)	4.273	2.615	GGAA17G05
D3S2418	3q28–29 (215.84)	4.325	2.678	ATA22E01
D5S2501	5q22.1 (116.98)	5.953	2.733	GATA68A03
D3S1311	3q29 (224.88)	4.282	2.950	AFM254VE1

Table 4 Most significant chromosomal regions showing African or European ancestry association with BMI

Location and distance (cM)	DNAME	Marker name	Estimated (r_l)
1q32.2–1q42.3			
226.16	Unknown	GATA124F08	−2.225
239.66	D1S549	GATA4H09	−2.036
247.23	D1S3462	ATA29C07	−2.167
254.64	D1S235	AFM203YG9	−2.168
3q28–29			
215.84	**D3S2418**	**ATA22E01**	**2.678**
224.88	**D3S1311**	**AFM254VE1**	**2.950**[b]
5q14.1–5q32			
85.25	D5S1501	GATA52A12	2.109
97.82	D5S1725	GATA89G08	2.369
116.98	**D5S2501**	**GATA68A03**	**2.733**
129.83	**D5S1505**	**GATA62A04**	**2.507**
139.33	**D5S816**	**GATA2H09**	**2.591**
147.49	D5S1480	ATA23A10	1.977
7p14.3–7p12.3			
50.29	D7S817	GATA13G11	−1.990
57.79	D7S2846	GATA31A10	−1.789[a]
69.56	D7S1818	GATA24D12	−2.008
15q25.3–q26.3			
82.84	**D15S655**	**ATA28G05**	**−2.493**
90.02	**D15S652**	**ATA24A08**	**−3.139**[b]
100.59	**D15S816**	**GATA73F01**	**−3.433**[b]
122.14	D15S642	GATA27A03	−2.120
16p13.1–16p11.2			
22.65	D16S748	ATA3A07	2.367
29.97	D16S764	GATA42E11	2.418
43.89	D16S403	AFM049XD2	1.899[a]
50.6	D16S769	GATA71H05	2.233
57.79	D16S753	GGAA3G05	2.270

Markers for which the r_l values are >2.5 are shown in boldface.
[a]Locus does not have $|r_l| > 1.96$ but is listed here because it lies between two points in the same region having $|r_l| > 1.96$. [b]Locus is significant after the permutation test.

Because of the strong sex effect on BMI in our sample, we also looked to see if there were sex differences in our ancestry mapping results. For the significant locations we identified, there were no significant differences in the regression estimates on local ancestry between men and women, as tested by an interaction term between sex and ancestry in the regression analysis. Hence, the effects we observed do not appear to be sex-specific.

DISCUSSION

This study represents the first large-scale attempt to identify loci underlying an obesity-related trait (BMI) by admixture mapping in AAs, and our results were quite promising. The ancestry *Z*-score distribution revealed outliers in both tails, but otherwise a good fit to a normal distribution. Table 4 lists 24 markers out of 284 (8.5%) compared to the expected 14 (5%). If we take $|r_l| > 2.5$ as our cutoff instead of 1.96, there are nine (3.2%) markers above that threshold although we expect only 3.5 (1.24%). If we look at the markers in Table 3 with further detail, we find that the markers are mostly clustered into six different regions of the genome (Table 4) at 1q, 7p, and 15q (excess African ancestry) and 3q, 5q, and 16p (excess European ancestry). Eight of the nine markers for which the r_l values are >2.5 (shown in boldface) are from the three regions, 15q25.3–q26.3, 3q28–q29, and 5q14.1–5q32.

Among the six identified locations, the regions 7p12.3–7p14.3 and 16p11.2–16p13.1 have the lowest statistical significance. However, the region on 7p is known to harbor the growth-related growth hormone–releasing hormone receptor (*GHRHR*) and isolated growth hormone deficiency (*IGHD*) genes. Mutations in these genes have been generally associated with lower BMI (24). Mouse polygenic models of obesity studying a quantitative trait locus for abdominal fat

have found a putative human homologue in region 7p13–p12 (ref. 25). It may be noted here that the r_l values of the region 7p are negative, implicating a positive association of BMI with excess African ancestry at that locus. In a recent linkage study among 769 subjects from 182 families in Africa, the marker D7S817 has been linked to BMI with a logarithm of odds (lod) score of 3.83 (ref. 26). In another linkage study consisting of 342 families, D7S1818 was associated with a lod score of 2.2 for BMI trends from childhood to adulthood (27). The marker D16S764, which has the highest r_l value of 2.41 among all the markers in the 16p region, has been shown previously to be both modestly linked (lod 2.45) and associated ($P < 0.0006$) with BMI (28). The sample in the above study was composed of 893 white sibpairs, which may be consistent with the high positive value of r_l. Several markers in this region have also been shown to be linked to BMI and other obesity-related phenotypes with lod scores ranging from 1.7 to 3.21. All these studies were reported among different populations of European descent (28,29).

The region 1q32.2–1q42.3 contains the angiotensinogen (*AGT*) gene. Numerous previous studies (30–33) have found association between this gene and obesity-related phenotypes, including BMI. Keeping in mind the negative r_l values of markers in this region (African excess), the fact that linkage of this region with obesity-related phenotypes was found only among black families may be of particular interest.

The six consecutive markers on chromosome five with high positive r_l values span a large region from 78 to 144 Mb (5q14.1–5q32). This region has been reported numerous times previously. For example, this region harbors the gene *PCSK1*, common polymorphisms in the gene have been associated with obesity (10). The second marker included in our study from this region, D5S1725 (with an r_l value of 2.37), was previously found to be linked to body fat and fat mass with lod scores of 2.56 and 2.25, respectively (34). It is worth mentioning that the study cohort consisted of 321 sibpairs from Western Africa. However, in two different linkage studies among white families, markers in this region, including D5S1505, which is included in our analysis, have been found to be linked with more direct BMI-related traits (27,35,36). Chen *et al.* (27) analyzed 342 sibships and found D5S1453 at 5q21.3 to be linked with trends in BMI from childhood to adulthood with a lod score of 2 and D5S1505 to be linked with long-term burden in BMI with a lod score of 2.2. The above mentioned study (35) included 447 French subjects in 109 pedigrees chosen through a proband with BMI >27. They found a linkage peak with lod score 2.68 at marker D5S1463, located at 5q14.3. Rice *et al.* (36) studied abdominal fat and high BMI, involving 453 subjects in 99 white families, and found two peaks in this region. Of these two locations, marker D5S658 at 5q31.3 had a lod score of 2.06 and D5S1480 had a lod score of 2.1. In another study involving 88 families, BMI was shown to be associated with polymorphisms in the gene nuclear receptor subfamily 3, group C, member 1 (glucocorticoid receptor) (*NR3C1*) at 5q31 with a *P* value of 0.009 (ref. 37).

The markers of chromosome 3, D3S2418 and D3S1311, spanning a 5 Mb region, show the strongest excess European ancestry with BMI in our study. Associations of markers in the candidate gene *apolipoprotein D* (3q26.2–qter) with BMI was reported by Vijayaraghavan *et al.* (38). Marker D3S1311, which was statistically significant after the permutation test, also lies in a promising linkage region (lod score 2.5) in the study of Rice *et al.* (36).

The region 15q25.3–15q26.3 harbors the two markers (D15S652 and D15S816) with the most significant r_l values in our study. It is also the site for the gene neuromedin B (*NMB*) (15q22–qter) which is a candidate for type 1 diabetes, obesity, and hunger disorder (39). Polymorphisms in *NMB* have been shown to be associated with BMI and other obesity-related phenotypes (40). In a recent study, Bouchard *et al.* (41) fine mapped a 20-Mb region around a quantitative trait locus on chromosome 15q26 for abdominal subcutaneous fat in an extended sample of 707 subjects from 202 families from the Quebec Family Study. Chagnon *et al.* (39) studied 336 sibpairs and 609 relative pairs and found D15S652 linked with fat free mass with a lod score of 3.56. Another marker in this region, D15S657 at 15q26.2, also had a lod score of 2. Using a subset of the data that we have analyzed here, Lewis *et al.* (42) have reported linkage (lod score 3) of body fat (%) with marker D15S655 among men in the HyperGEN network.

Although our results have identified specific locations that may harbor genes influencing the trait BMI, they cannot indicate the precise mechanism for the association. Specifically, they may represent genetic differences between Africans and Europeans in lean mass and bone content, or for patterns of fat accumulation. Because we did not have specific measures for these associated traits, we could not dissect more directly the source of the association.

We also note that obesity (or BMI) is a complex trait and it can respond to differential environmental influences. Though our study consists only of AA individuals, we still note a significant variation among networks indicating possible heterogeneities in the sample. The absence of detailed data on environmental influences, like diet, and its possible interaction with genetics influencing BMI are questions which are beyond the scope of this article.

To our knowledge, this is the largest quantitative admixture mapping effort in terms of sample size and marker locus involvement for the trait. We took care to eliminate possible errors in the locus-wise ancestry estimates, because any systematic bias could affect the final results. Statistical variation in locus-wise ancestry estimates was kept to a minimum by running the MCMC for a long period. To further check the robustness of our results, we also examined results of analyses based on different random selections of unrelated individuals from the AA families and obtained very similar results. Overall our findings are encouraging and provide regions for follow-up analyses of genes influencing BMI in these and other AA families.

SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at http://www.nature.com/oby

ACKNOWLEDGMENTS

The following investigators are associated with the Family Blood Pressure Program: GenNet Network: Alan B. Weder (Network Director), Lillian Gleiberman (Network Coordinator), Anne E. Kwitek, Aravinda Chakravarti, Richard S. Cooper, Carolina Delgado, Howard J. Jacob, and Nicholas J. Schork. GENOA Network: Eric Boerwinkle (Network Director), Tom Mosley, Alanna Morrison, Kathy Klos, Craig Hanis, Sharon Kardia, and Stephen Turner. HyperGEN Network: Steven C. Hunt (Network Director), Janet Hood, Donna Arnett, John H. Eckfeldt, R. Curtis Ellison, Chi Gu, Gerardo Heiss, Paul Hopkins, Aldi T. Kraja, Jean-Marc Lalouel, Mark Leppert, Albert Oberman, Michael A. Province, D.C. Rao, Treva Rice, and Robert Weiss. SAPPHIRe Network: David Curb (Network Director), David Cox, Timothy Donlon, Victor Dzau, John Grove, Kamal Masaki, Richard Myers, Richard Olshen, Richard Pratt, Tom Quertermous, Neil Risch, and Beatriz Rodriguez. National Heart, Lung, and Blood Institute: Dina Paltoo, and Cashell E. Jaquish. Web site: http://www.biostat.wustl.edu/fbpp/FBPP.shtml. This work was supported by grants awarded to the Family Blood Pressure Program, which is supported by a series of cooperative agreements from the National Heart, Lung and Blood Institute to GenNet, HyperGEN, GENOA, and SAPPHIRe. We thank Mark Kvale for his assistance with analysis and also two anonymous reviewers for their comments and suggestions.

DISCLOSURE

The authors declared no conflict of interest.

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