

A Genome-Wide Scan for Body Mass Index among Nigerian Families

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Abstract

ADEYEMO, ADEBOWALE, AMY LUKE, RICHARD COOPER, XIAODONG WU, BAMIDELE TAYO, XIAOFENG ZHU, CHARLES ROTIMI, NOURDINE BOUZEKRI, AND RYK WARD. A genome-wide scan for body mass index among Nigerian families. *Obes Res.* 2003; 11:266–273.

Objective: Interest in mapping genetic variants that are associated with obesity remains high because of the increasing prevalence of obesity and its complications worldwide. Data on genetic determinants of obesity in African populations are rare.

Research Methods and Procedures: We have undertaken a genome-wide scan for body mass index (BMI) in 182 Nigerian families that included 769 individuals.

Results: The prevalence of obesity was only 5%, yet polygenic heritability for BMI was in the expected range (0.46 ± 0.07). Tandem repeat markers (402) were typed across the genome with an average map density of 9 cM. Pedigree-based analysis using a variance components linkage model demonstrated evidence for linkage on chromosome 7 (near marker D7S817 at 7p14) with a logarithm of odds (LOD) score of 3.8 and on chromosome 11 (marker D11S2000 at 11q22) with an LOD score of 3.3. Weaker evidence for linkage was found on chromosomes 1 (1q21, LOD = 2.2) and 8 (8p22, LOD = 2.3). Several candidate genes, including neuropeptide Y, DRD2, APOA4, lamin A/C, and lipoprotein lipase, lie in or close to the chromosomal regions where strong linkage signals were found.

Discussion: The findings of this study suggest that, as in other populations with higher prevalences of obesity, positive linkage signals can be found on genome scans for obesity-related traits. Follow-up studies may be warranted to investigate these linkages, especially the one on chromosome 11, which has been reported in a population at the opposite end of the BMI distribution.

Key words: linkage, genetics, genome-wide scan, Nigeria

Introduction

Obesity is associated with a number of common disorders including diabetes, hyperlipidemia, and cardiovascular diseases. The prevalence of obesity is quite high in industrialized countries, whereas many developing countries are experiencing increases in the prevalence of obesity and its complications. Indeed, it has been noted that one consequence of the nutrition transition in developing countries is a rapid increase in obesity in association with a decline in undernutrition (1,2). Thus, obesity, which used to be regarded as a disease of affluent or industrialized countries, has become a major public health issue worldwide.

Genetic determinants of obesity are being sought using a wide variety of approaches, including studies of single-gene mutations, Mendelian disorders, quantitative trait loci (QTLs)¹ from cross-breeding experiments, association studies, and linkage studies in animal models and man. The evidence accumulated so far has been the subject of a number of published reviews (3–10). The latest reviews suggest that putative loci for obesity-related phenotypes can be found on every chromosome except Y (9). However, few of these findings have been replicated (10), whereas there have been a considerable number of negative studies (9). This outcome is not entirely unexpected because obesity is a complex phenotype that is influenced by multiple genetic and nongenetic factors.

Received for review June 28, 2002.

Accepted for publication in final form November 13, 2002.

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¹ Nonstandard abbreviations: QTL, quantitative trait locus; BMI, body mass index; NHLBI, National Heart, Lung, and Blood Institute; MGS, Mammalian Genotyping Service; LOD, logarithm of odds; NPY, neuropeptide Y.

Genome-wide scans, which make no assumptions about the genes of interest, are increasingly being used to study obesity. A number of such studies have been published for various obesity-related phenotypes, including body mass index (BMI), fat mass, skinfold thickness, percentage body fat, abdominal fat assessed by computerized tomography, blood lipids, and leptin (11–22). Few of these studies have been done in lean populations and virtually none in African populations. In this communication, we report a genome-wide scan for BMI in an African population that is lean, with a mean BMI of $\sim 21 \text{ kg/m}^2$ and prevalence of obesity $<5\%$ (23).

Research Methods and Procedures

Participant Recruitment

The study was carried out in Igbo-Ora, a rural community in southwest Nigeria comprised primarily of farmers from the Yoruba ethnic group. The sampling frame for this study was provided by the International Collaborative Study on Hypertension in Blacks, as described in detail elsewhere (24,25). Study protocols were reviewed and approved by the institutional review boards of the University of Ibadan and the Loyola University Medical Center. Written informed consent was obtained from the participants. Families were identified on the basis of a middle-aged proband, then his/her spouse and all available first-degree relatives were enrolled. Families that have a father, mother, and two or more offspring were genotyped in the genome scan. Half-siblings were encountered frequently due to polygyny and were enrolled whenever possible. The proband and family members enrolled were not identified based on any phenotypic obesity-related traits; however, probands with hypertension were over-sampled in the original study. Therefore, the data analysis was done with and without ascertainment correction.

Survey Methods

A screening examination was completed in a clinic setting by trained research staff using a standardized protocol (25). A medical history and pedigree were obtained. Height was measured to the nearest 0.1 cm using a stadiometer consisting of a steel tape attached to a straight wall and a wooden headboard. The headboard was positioned with the participant shoeless, feet and back against the wall, and head held in the Frankfort horizontal plane. Body weight was measured to the nearest 0.2 kg using calibrated electronic scales. BMI was calculated as weight (kilograms)/height² (meters²).

Laboratory Methods

Genomic DNA was extracted from the stored white cells and submitted for genotyping to the National Heart, Lung, and Blood Institute (NHLBI) Mammalian Genotyping Ser-

vice (MGS) (Marshfield, WI) (26). Tandem repeat markers were typed using the Marshfield “Set 10” panel of markers (<http://research.marshfieldclinic.org/genetics>). The mean heterozygosity for these markers as determined in this sample was 76%, compared with 74% reported by MGS, and the average inter-marker distance was $\sim 9 \text{ cM}$. During the preliminary analyses it was determined that four markers were much more commonly associated with Mendelian errors than were any of the others; it was inferred that genotyping errors for these markers were common and those four markers were excluded from further analyses.

Statistical Analysis

Both “ASPEX” (27) and “RELTEST” (28) were used to check the consistency of the pedigrees. After resolution of all instances of non-paternity and other errors in the family structures, further isolated Mendelian errors were identified with “PedCheck” (29) and linkage analysis programs. These errors were assumed to have occurred in the genotyping process and the associated markers were set to missing among the appropriate family members. Half-siblings were retained for the analysis.

BMI was used as a continuous trait. Heritability of BMI was estimated under a polygenic model using a variance components method as implemented in the SOLAR software package (30). We have reported previously the heritability of obesity-related traits from the parent study (31); in that study, heritability of BMI in Nigerians was 0.49 (± 0.05). Heritability was estimated with age (up to the second polynomial), sex, and all interactions between the age and sex terms as covariates. The linkage analysis was built on this initial polygenic heritability analysis.

Multipoint linkage analysis was undertaken using the SOLAR software package version 1.7.4 (30), which determines whether genetic variation at a specific chromosomal location can explain the variation in the phenotype. In this analysis, a variance component model applied to extended family data were used to test for evidence of linkage of QTLs for BMI. Variation in BMI was partitioned into components attributable to the additive variance of the QTL, additive polygenic variance, and random environmental variance. The residual heritability was modeled as a function of the expected genetic covariances between relatives, whereas the QTL effect was modeled as a function of the identity-by-descent relationships at the marker locus. The null hypothesis tested was that the additive genetic variance equals zero (no linkage) and this was done by comparing the likelihood of this restricted model with that of a model in which additive genetic variance is estimated. The difference between the two \log_{10} likelihoods produces a logarithm of odds (LOD) score that is equivalent to the classical LOD score of linkage analysis. Twice the difference in \log_e likelihoods of these models yields a test statistic that is asymptotically distributed as a 50:50 mixture of a

Table 1. Distribution of relative pairs in Nigerian families available for genome scan analysis

Relationship	Number of pairs
Parent-offspring	555
Sibling	234
Half-sibling	139
Avuncular	108
Grandparent-grandchild	27
Half-avuncular	51
First cousins	7
Great avuncular	1

χ^2 variable and a point mass at zero. In each model, simultaneous adjustment was done for age, sex, and age². One-unit LOD support intervals were obtained by identifying the peaks for the maximum LOD score on the plot of the multipoint results, dropping down one LOD unit, and finding the chromosomal region defined by the shoulders of the curve (32). Multipoint LOD scores as well as one LOD unit support intervals are reported for regions that showed evidence for linkage. The MGS sex-averaged map distances were used in the linkage analysis.

Results

A total of 182 families comprising 769 individuals were studied. The types of relationships and the frequencies of relative pairs are shown in Table 1.

The descriptive characteristics of the study sample are shown in Table 2. Age ranged from 13 to 90 years with a mean of 41 years. Men were significantly taller than women but there were no significant differences in weight or in systolic and diastolic blood pressures. The population was quite lean with a mean BMI of 21.3 (± 4.4) kg/m²; the range of BMI among persons over the age of 20 years extended from 14 to 44 kg/m². The distribution of BMI was modestly right-skewed, although a few individuals were quite obese (Figure 1). At the same time, based on the definition of a BMI < 18.5 kg/m² as chronic energy deficiency, 10.4% of the sample were undernourished. Women had a higher mean BMI than men (22.3 vs. 20.4 kg/m²) and a correspondingly higher prevalence of obesity. BMI was positively correlated with age ($r = 0.25$, $p < 0.001$); this correlation was slightly higher among men ($r = 0.30$, $p < 0.001$) than among women ($r = 0.22$, $p < 0.001$).

Familial correlations for age- and sex-adjusted BMI were 0.24 (± 0.05) for parent-offspring pairs, 0.20 (± 0.07) for sibling pairs, and 0.14 (± 0.10) among half-sibling pairs. Age, age², and sex accounted for 23.1% of the total phenotypic variance. Maximum likelihood heritability for BMI

Table 2. Descriptive characteristics of Nigerian family members

Characteristic	Mean (SD)		
	Men (n = 414)	Women (n = 355)	All (n = 769)
Age (years)	41.6 (20.4)	41.3 (18.3)	41.5 (19.5)
Weight (kg)	56.5 (12.9)	55.6 (13.1)	56.1 (13.0)
Height (cm)*	166.0 (9.7)	157.9 (7.6)	162.2 (9.7)
BMI (kg/m ²)*	20.4 (3.8)	22.3 (4.9)	21.3 (4.4)
Systolic blood pressure	126.8 (27.2)	128.5 (29.0)	127.6 (28.1)
Diastolic blood pressure	76.1 (18.2)	78.3 (18.1)	77.1 (18.1)
% BMI \geq 30 kg/m ² *	2.0	8.1	4.9

* Male-female differences significant at $p < 0.05$.

under a polygenic model was 0.46 (± 0.08) after adjusting for age, age², and sex, indicating that a substantial proportion of the variation in BMI is due to the additive effect of genes. The graphical results for the whole-genome scan are presented in Figure 2 and the maximum multipoint LOD scores are shown in Table 3. The highest LOD scores were obtained on chromosome 7 (D7S817 at location 50 cM with an LOD of 3.83) (Figure 3A) and chromosome 11 (D11S2000 at location 101 cM with an LOD of 3.35) (Figure 3B). Weaker linkage signals with an LOD of over 2 were seen on chromosomes 1 (D1S534 at location 152 cM, LOD 2.24) and 8 (GATA151F02 at location 27 cM, LOD 2.34). Reanalyzing the data with the log transformation of

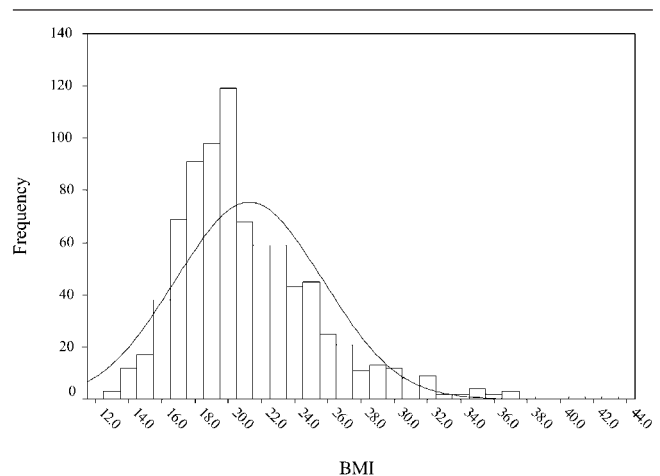


Figure 1: Distribution of BMI.

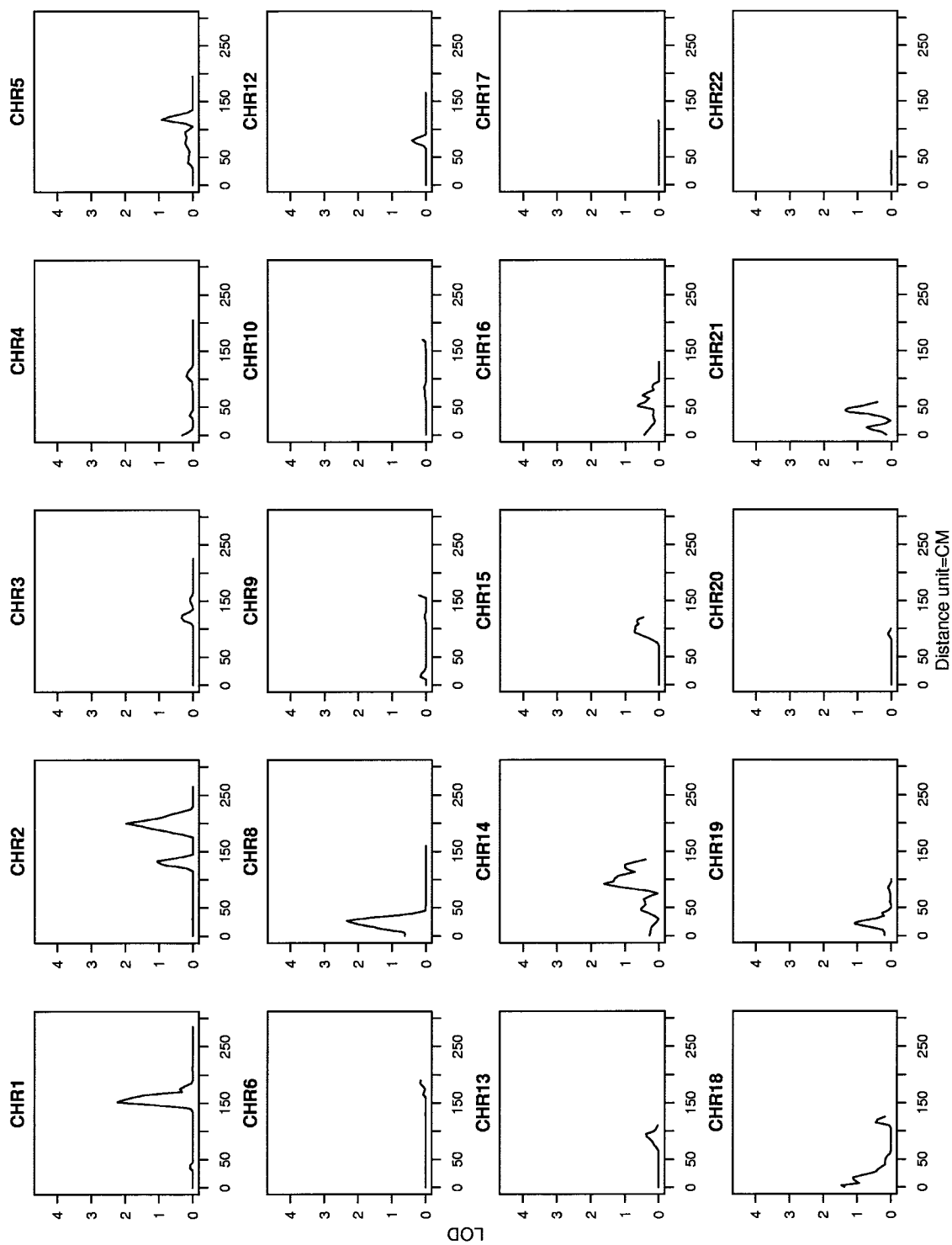


Figure 2: Genome-wide LOD scores for BMI on all autosomes, except chromosomes 7 and 11, using SOLAR.

Table 3. Maximum LOD scores from multipoint linkage analysis

Chromosomal region	Genomic marker	Location (cM)	LOD score	One LOD unit support interval (cM)
LOD > 3.0				
7p14	D7S817	50	3.83	45 to 63
11q22	D11S2000	101	3.35	97 to 110
LOD > 2.0				
				148 to
1q21	D1S534	152	2.24	165
8p22	GATA151F02	27	2.34	13 to 34

BMI as the phenotype led to the same conclusions but with slightly lower LOD scores. With the transformation, the LOD scores were 3.07 for the locus on chromosome 7 at 50 cM, 2.72 for chromosome 11 at 101 cM, 2.24 for chromosome 1 at 152 cM, and 2.12 for chromosome 8 at 27 cM. Similar results were obtained after eliminating the four participants with a BMI > 4.5 SDs above the mean (LOD score for chromosome 7 = 3.3 and remained unchanged for the other chromosomes). After a reanalysis of the data with proband ascertainment adjustment to take account of the effect of ascertainment for high blood pressure in the parent study, the LOD scores were not altered.

Discussion

Although the environmental determinants of obesity, most prominently diet and physical activity, are relatively well characterized, the genetic determinants are only slowly being understood. Various approaches in mapping the genes conferring susceptibility to obesity have been utilized and rapid progress has been made in the last few years. The application of genome-wide scans to mapping the loci that are associated with obesity has been a major development in the field. To our knowledge, this is the first genome-wide scan for an obesity-related trait in an African population. More importantly, this population differs from most previously studied populations in that the prevalence of obesity is low. The prevalence of obesity (BMI \geq 30 kg/m²) is <5% and mean BMI is 21.5 kg/m², in contrast to other reports where the mean BMI is generally 27 kg/m² and above. Thus, this study represents the opposite end of the spectrum of BMI distribution from the previous genome-wide studies of obesity-related traits.

Significant linkage for BMI was found on chromosomes 7 and 11. The locus on chromosome 11 (11q22 at marker

D11S2000) has been shown previously to be linked to body fat among Pima Indians by Norman et al. (33). It should be noted, however, that the phenotype used in that study was percentage body fat, although the correlation between the two measures is high. Another marker, D11S912 located on 11q24, has been shown to be strongly linked to BMI (LOD = 3.6) among Pima Indians by Hanson et al. (12). However, this marker is ~30 cM distant from D11S2000. More recently, Feitosa et al. (21) found strong evidence for linkage for BMI on chromosome 7q32.3 at 137 cM (LOD 4.9 for all the population samples in that study combined). Therefore, the finding in this study suggests that the regions in question on chromosomes 7 and 11 may well harbor a QTL for obesity.

Each of the four markers with the maximum LOD scores in this study is located in, or close to, a chromosomal region where candidate genes that have shown linkage and/or association with obesity-related phenotypes have been identified. The marker on chromosome 7 (D7S817) lies in 7p14, adjacent to the chromosomal region where the neuropeptide Y (NPY) gene is located on 7p15.1. NPY has been shown to be linked to obesity and principal components of height, weight, skinfolds, and abdominal and hip circumferences (34); it is also associated with BMI and waist-to-hip ratio (35). The marker on chromosome 11 (D11S2000) lies in the same chromosomal region (11q22) where the dopamine D2 receptor gene DRD2 is located and is close to 11q23 where the apolipoprotein A-IV (APOA4) gene is located. DRD2 polymorphisms are strongly associated with relative weight (36), iliac and triceps skinfolds (37), obesity defined as BMI > 30 kg/m² (38), and energy expenditure (39), whereas APOA4 polymorphisms are associated with BMI, waist-to-hip ratio, and percentage of fat (40,41). The candidate genes on chromosomes 1 and 8 close to the markers with significant linkage in this study are the lamin A/C gene in region 1 q21.2-q21.3 and the lipoprotein lipase gene in 8p22. Polymorphisms of both genes have been shown to be associated with BMI (42–44).

Relative to other complex traits, genome-wide scans for obesity have begun to demonstrate reasonable consistency. For BMI, a locus on chromosome 10p first reported by Hager et al. (13) was replicated by Lee et al. (14), whereas a finding on 20q first reported by Norman et al. (32) was replicated by Lee et al. (14). More recently, a locus on 3q27 where linkage was first reported by Kissebah et al. (32) was identified in African Americans by Zhu et al. (22). This locus has since been replicated in a large meta-analysis (45). However, in the recent genome-wide scan for obesity in African Americans (22), evidence of linkage of BMI was also found for markers on chromosomes 3 (D3S2427) and 5 (D5S817); these markers showed an LOD score of essentially zero in the present study. Likewise, we did not replicate the earlier finding by Rotimi et al. (46) among African Americans of linkage on chromosome 2, although it should

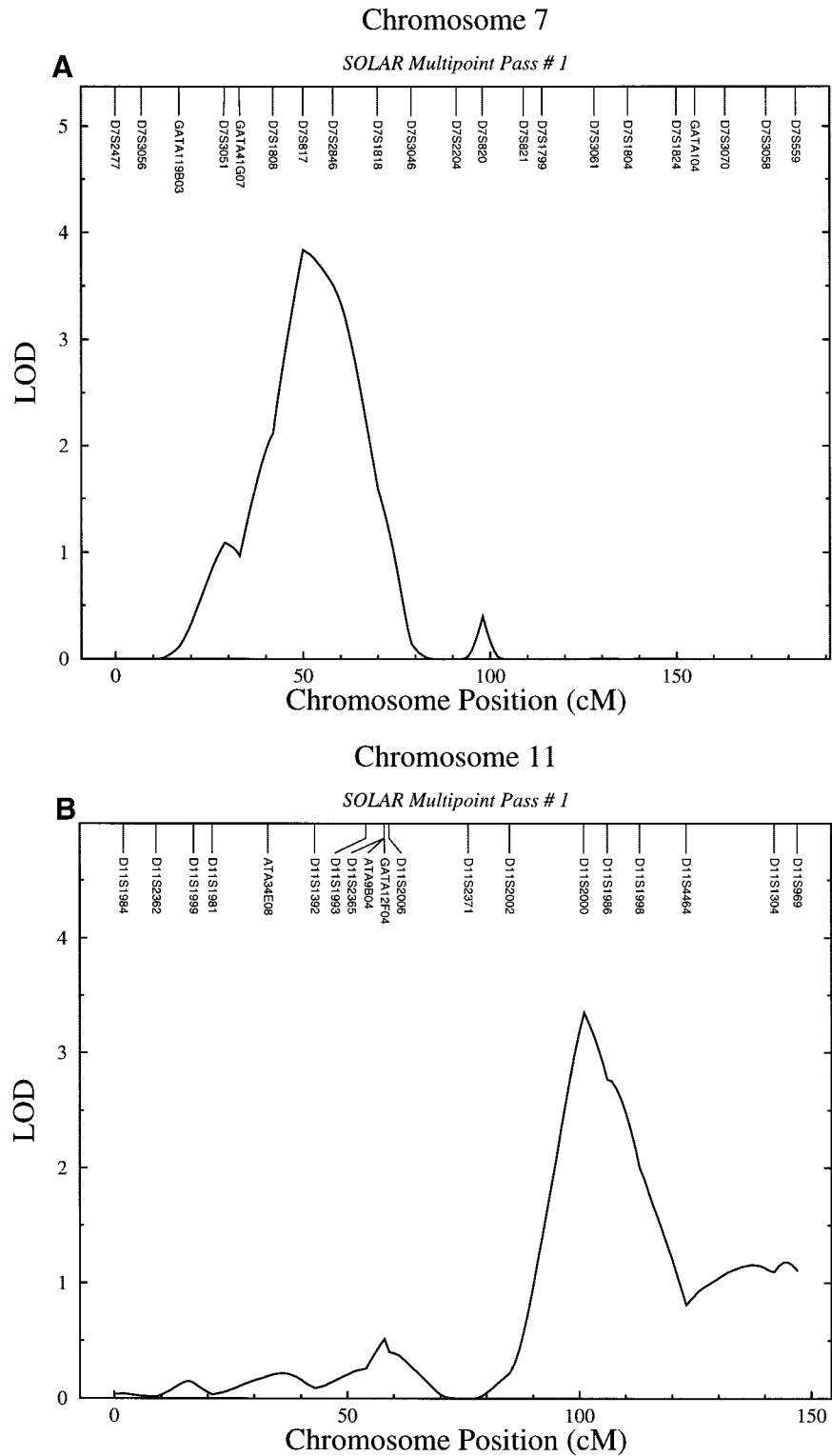


Figure 3: Multipoint linkage analysis for chromosome 7 (A) and chromosome 11 (B).

be noted that the phenotype in that study was serum leptin concentration. Further inspection of the results from these studies of African Americans did not reveal secondary

peaks (i.e., $LOD \geq 1.0$) that were shared with the present Nigerian sample. Two recent reports focused on patients with anorexia (47) and a similarly lean population in China

(48). The linkage evidence obtained in these studies (e.g., on chromosomes 4 and 2, respectively) was not identified in our data.

Genome-wide scans and other genetic studies for complex traits of African-origin populations are still uncommon. Such studies are needed given the high degree of genetic diversity among African populations and the potential for additional new information in contrasting environmental settings. Many African societies still experience low levels of chronic conditions such as obesity, diabetes, and hypertension relative to other societies. It could be argued that by studying this environment where the variation in lifestyle exposures are more limited among individuals it may be easier to identify genes linked to many complex traits if the genetic component of total variance is relatively larger. On the other hand, a potential weakness of our study sample is the inclusion of a small number of individuals who were undernourished.

In conclusion, we have reported the findings of a genome-wide scan for BMI in Nigerian families in a population that is lean (mean BMI ~ 21 kg/m²; prevalence of obesity $\sim 5\%$) relative to other populations. Pedigree-based analysis using a variance components linkage model demonstrated evidence for linkage on chromosome 7 (near marker D7S817 at 7p14) with an LOD score of 3.8 and on chromosome 11 (marker D11S2000 at 11q22) with an LOD score of 3.3. Weaker evidence for linkage (LOD >2) was found on chromosomes 1 (1q21, LOD = 2.2) and 8 (8p22, LOD = 2.3). The locus on chromosome 11 has been shown previously to be linked to body fat among Pima Indians. Several candidate genes, including NPY, DRD2, APOA4, lamin A/C, and lipoprotein lipase, lie in or close to the chromosomal regions where strong linkage signals were found. The findings suggest that, as in other populations with higher prevalences of obesity, positive linkage signals can be found on genome scans for obesity-related traits. Follow up studies may be warranted to investigate these linkages, especially the one on chromosome 11.

Acknowledgments

This work was supported by grants from the NHLBI (HL45508 and HL47910). Genotyping was done by the NHLBI MGS (Marshfield Medical Research Foundation, Marshfield, WI). Some of the results of this paper were obtained using the program S.A.G.E., which is supported by a U.S. Public Health Service Resource Grant (RR03655) from the National Center for Research Resources.

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