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A genome-wide linkage scan for dietary energy and nutrient intakes: the Health, Risk Factors, Exercise Training, and Genetics (HERITAGE) Family Study[1–3]

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ABSTRACT

Background: A poor diet is a risk factor for chronic diseases such as obesity, cardiovascular disease, hypertension, and some cancers. Twin and family studies suggest that genetic factors potentially influence energy and nutrient intakes.

Objective: We sought to identify genomic regions harboring genes affecting total energy, carbohydrate, protein, and fat intakes.

Design: We performed a genomic scan in 347 white sibling pairs and 99 black sibling pairs. Dietary energy and nutrient intakes were assessed by using Willett's food-frequency questionnaire. Single-point and multipoint Haseman-Elston regression techniques were used to test for linkage. These subjects were part of the Health, Risk Factors, Exercise Training, and Genetics (HERITAGE) Family Study, a multicenter project undertaken by 5 laboratories.

Results: In the whites, the strongest evidence of linkage appeared for dietary energy and nutrient intakes on chromosomes 1p21.2 ($P = 0.0002$) and 20q13.13 ($P = 0.00007$), and that for fat intake appeared on chromosome 12q14.1 ($P = 0.0013$). The linkage evidence on chromosomes 1 and 20 related to total energy intake rather than to the intake of specific macronutrients. In the blacks, promising linkages for macronutrient intakes occurred on chromosomes 12q23-q24.21, 1q32.1, and 7q11.1. Several potential candidate genes are encoded in and around the linkage regions on chromosomes 1p21.2, 12q14.1, and 20q13.13.

Conclusions: These are the first reported human quantitative trait loci for dietary energy and macronutrient intakes. Further study may refine these quantitative trait loci to identify potential candidate genes for energy and specific macronutrient intakes that would be amenable to more detailed molecular studies. *Am J Clin Nutr* 2004;79:881–6.

KEY WORDS Gene, quantitative trait locus, inheritance, food preference, linkage, energy intake

INTRODUCTION

A poor diet is a risk factor for several major chronic diseases, including obesity, cardiovascular disease, hypertension, type 2 diabetes, and cancer. High dietary fat tends to cause a high energy intake, which can lead to weight gain and obesity (1). Dietary fat has been associated with obesity in population studies (2–7). Taste preference, a determinant of food selection, has also been associated with weight gain and obesity (4, 8).

Some evidence indicates that genetic factors contribute to individual differences in energy and nutrient intakes. Studies have reported familial resemblance in nutrient intakes (9, 10), whereas twin studies have shown that monozygotic twins are more alike in their diets than are dizygotic twins (11). Evidence exists for a genetic influence on the selection of some foods, especially those with a bitter taste (12). The preference for a given macronutrient is in part heritable (4), and several researchers found significant heritability coefficients for carbohydrate and lipid intakes (11, 13, 14).

A number of neuropeptides, hormones, and their receptors have been shown to be potential regulators of food intake (2, 15). Little is known about the effect of DNA sequence variation in such genes on energy and macronutrient intakes. Bachmanov et al (16) described 2 quantitative trait loci (QTLs) on mouse chromosome 4 that were responsible for $> 50\%$ of the genetic variability in sucrose intake. In humans, data on genes' influence on diet intake remain scarce. Recently, Steinle et al (6) reported on eating behavior in an Old Order Amish population. They measured 3 eating behaviors—restraint, disinhibition, and hunger—and found evidence of a genetic component to these eating behaviors, by both linkage and heritability estimates.

The objective of the present study was to identify chromosomal regions containing genes that affect dietary energy and macronutrient intakes in healthy but sedentary subjects. We per-

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formed a genome-wide linkage scan in 225 families for total dietary energy intake and consumption of carbohydrate, protein, fat, and sucrose, by using data on blacks and whites from the Health, Risk Factors, Exercise Training, and Genetics (HERITAGE) Family Study.

SUBJECTS AND METHODS

The study cohort consisted of 514 white subjects (253 men and 261 women) from 99 nuclear families and 313 black subjects (110 men and 213 women) from 126 family units of the HERITAGE Family Study. Conducted by a consortium of 5 universities in the United States and Canada, the study has as its primary goal to document the role of the genotype in the cardiovascular, metabolic, and hormonal responses to aerobic exercise training. Sedentary subjects were recruited at 4 clinical centers: the University of Texas (Austin), Laval University (Montreal), the University of Minnesota (Minneapolis), and Indiana University (Bloomington, IN; moved from Arizona State University when one of the principal investigators changed affiliations), and the data coordinating center was located at Washington University (St Louis). Subjects ranged in age from 17 to 65 y, and the maximum number of sibling pairs available was 347 in the whites and 99 in the blacks. The study design and inclusion criteria were described elsewhere (17). Subjects were required to be in good health (ie, free of diabetes, cardiovascular diseases, or other chronic diseases) and to have been sedentary (ie, no regular physical activity) for the previous 6 mo. The study protocol was approved by the institutional review boards of each institution in the HERITAGE Family Study research consortium, and all subjects gave written informed consent.

Dietary intake of nutrients

Total energy (in kJ), protein, fat, carbohydrate, and sucrose intakes served as dietary phenotypes. Macronutrient intakes were analyzed either in absolute value (g) or as a percentage of total energy intake. Dietary intake data were derived from Willett's food-frequency questionnaire (FFQ; 18), which was self-administered by study subjects and was then reviewed by an interviewer with each subject at a HERITAGE Family Study clinical center. The questionnaire listed $>$ 90 food items and asked subjects how often, on average, they consumed the specified portion sizes of each food during the past year. There were 9 possible responses, ranging from "never" to "$\geq$ 6 times/d." Scoring of nutrient and energy intakes was performed according to the procedure described by Willett et al (18) at the Harvard School of Public Health FFQ Scoring Center. Correlation coefficients ranging from 0.43 for total energy to 0.59 for protein (as % of energy) were found between daily energy and nutrient intake derived from food records and FFQ nutrient scores (18).

Markers and genotyping

We used 509 markers covering all of the autosomes with an average spacing of 6.0 megabases (Mb). Microsatellites were selected mainly from the Marshfield panel (version 8a; Center for Medical Genetics, Marshfield Medical Research Foundation, Marshfield, WI; Internet: http://www.research.marshfieldclinic.org/genetics/) and from the Genetic Location Data Base (Genetic Epidemiology Research Group, Human Genetic Division, University of Southampton, Southhampton, United Kingdom; Internet: http://www.cedar.genetics.soton.ac.uk). Map locations were determined from the Genetic Location Data Base maps. Polymerase chain reaction conditions and marker typing were described previously (19). Automatic DNA sequencers from Li-Cor (Lincoln, NE) were used to detect the polymerase chain reaction products. An electronic image of the gel was produced and used for genotyping with the use of SAGA software (version 2.1; Li-Cor). After manual editing of the typing, results were exported to a local dBase IV database (GENEMARK; Pennington Biomedical Research Center, Baton Rouge, LA). Incompatibilities with Mendelian inheritance were checked, and families showing incompatibilities were completely regenotyped: $<$ 10% of the subjects were retyped.

Statistical analyses

Each dietary intake phenotype was tested separately for normal distribution in the blacks and the whites. A log transformation was performed for phenotypes that did not meet the criterion of normality (skewness and kurtosis: $<$ 1). Phenotypic characteristics and dietary intakes were compared between the 2 ethnic groups by using the general linear model procedure of SAS software (version 8.1; SAS Institute Inc, Cary, NC). Normally distributed phenotypes were adjusted for age (up to cubic polynomial), sex, and height by using stepwise multiple regression procedures separately in each of the 8 race-by-sex-by-generation subgroups. To identify the most meaningful body size covariates for the adjustment procedure, partial correlations (adjusted for age) were calculated between dietary phenotypes and height, weight, body mass index (in kg/m^2), and body surface area. Height had the strongest correlations with most of the dietary phenotypes. The residuals of dietary phenotypes from the stepwise regression procedures were standardized to a mean zero and unit variance within each subgroup and then constituted the variables for linkage analysis. All statistical procedures described above were done by using SAS statistical software (version 8.1; SAS Institute Inc).

Both single-point and multipoint linkage analyses based on Haseman-Elston regression techniques were performed to test for linkage between the marker locus and a putative gene that influenced the adjusted phenotype by using the SIBPAL program of SAGE software (version 4.0; 20). Phenotypic resemblance of siblings expressed as the mean-corrected trait product of the siblings' trait value was linearly regressed on the estimated proportion of alleles shared identically by descent (IBD) by siblings at each marker locus. Single-point and multipoint IBD estimates were generated by using the GENIBD program of the SAGE software. Separate linkage analyses were conducted in the blacks and the whites. P values of 0.00074 (logarithm of odds score = 2.2) and 0.000022 (logarithm of odds score = 3.6) were required to claim suggestive and significant linkages, respectively (21). The tolerance level was decreased from one false-positive response per 20 genome scans to one false-positive response per single scan, as proposed by Rao and Province (22), to identify promising linkages (P = 0.0023, logarithm of odds score = 1.75).

RESULTS

The distribution of sibship size is shown in **Table 1**. Sibship size was smaller in the blacks than in the whites. Dietary intake data for the 2 ethnic groups are presented in **Table 2**. The groups were not markedly different in macronutrient and energy intakes, but there was a significantly higher degree of heterogeneity in the

TABLE 1
Distribution of sibship sizes among the blacks and the whites in the HERITAGE Family Study[1]

No. of children	No. of families	
	Blacks	Whites
1	46	1
2	63	8
3	14	63
4	3	22
5	—	3
6	—	2
Total	126	99

[1] HERITAGE, Health, Risk Factors, Exercise Training, and Genetics.

blacks. The only significant intake difference between the 2 groups was that for sucrose intake, which was significantly higher in the blacks.

Linkage results are summarized in **Table 3** for the whites and in **Table 4** for the blacks. Significant linkages were observed mainly on chromosomes 1 and 20 in the whites. A chromosomal region linked to energy and fat intake phenotypes was uncovered in chromosome 1 (1p22.1-1q22). The strongest evidence of linkage was detected at marker D1S1631 ($P = 0.00002$ for fat, $P = 0.0002$ for energy), and several suggestive or promising linkages

TABLE 2
Phenotypic characteristics and dietary energy and nutrient intakes in the HERITAGE Family Study[1]

Phenotype	Blacks ($n = 313$)	Whites ($n = 514$)
Age (y)	35.2 ± 11.6	35.6 ± 15.5[2]
Height (m)	1.67 ± 9.18	1.71 ± 9.47[3]
BMI (kg/m^2)	28.0 ± 6.13	25.8 ± 4.96[3]
Total energy		
(kJ)	9497.7 ± 5443.4	10 681.7 ± 3803.3
(kcal)	2270.0 ± 1301.0	2253.0 ± 909.0
Carbohydrate		
(% of energy)	53.1 ± 9.1	52.1 ± 7.5
(g)	304.4 ± 191.3	293.4 ± 124.4
Protein		
(% of energy)	16.7 ± 3.7	16.4 ± 2.9
(g)	93.2 ± 54.5	91 ± 35
Fat		
(% of energy)	30.9 ± 6.5	31.3 ± 5.7
(g)	77.5 ± 47.2	79.1 ± 38.2
Sucrose		
(% of energy)	11.3 ± 3.5	9.6 ± 3.1[3]
(g)	64.6 ± 42.6	54.8 ± 32.6[3]

[1] All values are least-square $\bar{x}$ ± SD. HERITAGE, Health, Risk, Factors, Exercise Training, and Genetics; BSA, body surface area.
[2,3]Significantly different from the blacks: [2]$P = 0.005$, [3]$P = 0.0001$.

TABLE 3
Results from single-point (SL) and multipoint (ML) linkage analyses for dietary intake phenotypes in the whites derived by using SIBPAL[1]

			Phenotypes[3]									
			Total energy (kJ)		Carbohydrate (g)		Fat (g)		Protein (g)		Protein (%)	
Region	Marker	Map position[2]	SL	ML	SL	ML	SL	ML	SL	ML	SL	ML
1p32.3	EDN2	54.868	—	—	—	—	—	0.0035	—	—	—	—
1p32.3	D1S193	56.093	—	0.009	—	—	—	0.007	—	—	—	—
1p32.2	DIS197	58.439	0.005	0.01	0.0039	0.007	—	—	—	—	—	—
1p22.3	D1S198	88.650	0.002	0.01	0.0062	0.0053	—	—	—	—	—	—
1p22.3	D1S551	97.854	—	0.0005	—	0.0003	—	0.002	—	0.005	—	—
1p21.3	D1S1588	102.150	—	0.0027	—	0.0035	—	0.007	—	—	—	—
1p21.2	D1S1631	106.989	0.006	0.0002	0.0037	0.0026	0.0007	0.00002	—	—	—	—
1p13.2	AMPD1	116.104	—	0.0005	—	—	—	0.00006	—	—	—	—
1p11.2	D1S534	125.032	—	0.0008	—	—	—	0.00038	—	—	—	—
1q12	D1S2222	139.857	—	—	—	—	—	0.0002	—	—	—	—
1q21.1	D1S394	150.991	—	—	—	—	0.0020	0.00081	—	—	—	—
1q21.2	S100A1	154.041	—	—	—	—	—	0.001	—	—	—	—
1q22	D1S1653	162.743	—	—	—	—	0.0037	0.0033	—	—	—	—
4q21.1	D4S1534	131.600	—	—	—	—	—	—	—	—	0.0021	0.0090
4q22.1	D4S1647	145.080	—	—	—	—	—	—	—	—	0.0062	0.0032
6q16.3	D6S1056	106.607	—	—	—	—	—	—	—	—	0.0071	0.0065
7q31	D7S3061	132.182	0.009	0.0080	—	—	0.0063	0.0069	—	—	—	—
8q23.3	D8S1132	123.799	—	—	—	—	—	—	—	—	0.0098	0.0071
12q14.1	D12S1691	68.940	—	—	—	—	0.00002	0.0013	—	—	—	—
13q31.3	D13S317	85.065	—	—	—	—	—	—	—	—	0.0028	0.0035
20q13.13	D20S887	54.853	0.006	0.0030	—	—	0.0099	0.0093	—	—	—	—
20q13.13	D20S869	57.290	0.0002	0.0001	0.0011	0.0023	0.0026	0.0005	0.0001	0.00009	—	—
20q13.13	D20S857	59.068	0.0004	0.00007	0.0044	0.0008	0.0021	0.0006	0.0005	0.00022	—	—
20q13.13	D20S839	59.069	0.0003	0.00014	0.0035	0.0009	0.0048	0.0019	0.0088	0.00041	—	—
20q13.13	D20S480	59.274	0.0003	0.00013	0.0009	0.0006	0.0086	0.0016	0.0002	0.0009	—	—
20q13.13	D20S876	59.896	0.00007	0.00012	0.0004	0.001	0.0023	0.0027	0.0006	0.00085	—	—

[1] SIBPAL, a software program of the SAGE software package (20).
[2] Map position is a composite location in megabases constructed by the Location Data Base program from all physical and genetic data for each locus.
[3] Only P values ≤ 0.01 are presented.

TABLE 4
Results from single-point (SL) and multipoint (ML) linkage analysis for dietary intake phenotypes in the blacks derived by using SIBPAL[1]

			Phenotype[3]									
			Carbohydrate (% of energy)		Fat (% of energy)		Protein (% of energy)		Sucrose (g)		Sucrose (% of energy)	
Region	Marker	Map position[2]	SL	ML	SL	ML	SL	ML	SL	ML	SL	ML
1p22.3	LEPR	87.768	—	—	0.002	0.01	—	—	—	—	—	—
1q31.3	D1S1171	211.072	—	—	—	—	0.0002	0.0081	—	—	—	—
1q32.1	D1S249	216.600	—	—	—	—	0.0082	0.0027	—	—	—	—
1q32.1	D1S456	218.259	—	—	—	—	0.0061	0.0021	—	—	—	—
1q43	D1S517	254.465	—	—	—	—	—	—	0.002	0.0018	—	—
1q44	D1S204	260.704	—	—	—	—	—	—	0.004	0.0054	—	—
5q31.3	D5S436	152.500	—	—	—	—	0.0091	0.0032	—	—	—	—
6p21.1	D6S1017	42.406	—	—	—	—	—	—	—	—	0.004	0.002
6q22.31	D6S1040	128.160	—	—	0.002	0.004	—	—	—	—	—	—
7q11.1	D7S3046	67.065	—	—	—	—	0.0005	0.0012	—	—	—	—
12q23.3	IGF1	108.946	0.009	0.0027	—	—	0.0016	0.0009	—	—	—	—
12q24.21	D12S2070	121.952	0.003	0.0042	0.003	0.002	—	—	—	—	—	—
13q32.1	D13S793	95.753	—	—	—	—	—	—	—	—	0.002	0.007
20q13.12	D20S174	50.618	—	—	—	—	0.0064	0.0092	—	—	—	—

[1] SIBPAL, a software program of the SAGE software package (20).
[2] Map position is a composite location in megabases constructed by the Location Data Base program from all physical and genetic data for each locus.
[3] Only P values ≤ 0.01 are presented.

with markers AMPD1, D1S551, D1S394, S100A1, and D1S534 were detected. The size of this chromosomal region is large, as shown in **Figure 1**. Suggestive or promising linkages were observed also for total energy and carbohydrate intakes on chromosome 1p22-1p32 (54.8–88.6 Mb). On chromosome 12q14.1, marker D12S1691 had a promising ($P = 0.0013$) linkage with fat intake in the whites.

Suggestive or promising linkages for total energy intake, as well as for fat, carbohydrate, and protein intakes, were found on chromosome 20q13.13 in the whites (Table 3). Five markers showed consistent linkages for total energy and individual macronutrient intakes. The strongest linkage for total energy intake was observed at marker D20S857 ($P = 0.00007$), whereas marker D20S480 had the highest peak of linkage with carbohydrate intake. Linkages for fat intake ($P = 0.0005$), and protein intake ($P = 0.00009$) were observed at marker D20S869, which is ≈2 Mb from the preceding markers. The linkage analyses for energy nutrient phenotypes were repeated after additional adjustment for total energy intake. The linkages on chromosomes 1p22-q22 and 20q13.3 disappeared after adjustment, which indicated that the energy nutrient QTLs reflected total food consumption rather than nutrient-specific linkages (Figure 1).

Some promising linkages were found in the blacks. Both single-point and multipoint techniques found a promising linkage for sucrose intake on chromosome 1q43-44 at D1S517 ($P = 0.002$ and $P = 0.0018$, respectively). Promising linkages for energy intake derived from lipids were found on chromosomes 1p22.3 at LEPR, 6q22.31 at D6S1040, and 12q24.21 at marker D12S2070 (Table 4).

DISCUSSION

This study provides evidence that several QTLs contribute to variations in dietary energy and macronutrient intakes. Chromosomal regions 1p21.2-1q21.2, 12q14.1, and 20q13.13 were found to have the most significant linkage relations with dietary intake phenotypes. The evidence was weaker in the blacks, and that difference had to do with phenotypes and genomic regions that were different from those of the whites. Such a discordance can undoubtedly be accounted for in part by differences in both sibship size and the overall sample size between the 2 ethnic groups. However, these differences could also be genuine, because the linkage results for complex phenotypes have been inconsistent among ethnic groups, as reported also in other studies (23, 24).

The significant linkage identified at region 12q14.1 with marker D12S1691 was with fat intake. This marker is 0.02 Mb distant from the *LRP1* gene encoding the LDL receptor–related protein 1 known to bind to apolipoprotein E–containing lipoproteins. The significant linkage with D1S1631 for fat, carbohydrate, and total energy intakes is of considerable interest. The marker is located in the vicinity of the cluster of α-amylase genes—*AMY2A*, *AMY2B*, and *AMY1A*—that are involved in the digestion of starch (25). After adjustment of fat intake for total energy intake, the significant linkage region became insignificant (dotted line in Figure 1A), which suggested that the QTL was for total food intake rather than for fat alone.

Strong and consistent linkages were found in region 20q13.13 for total energy and macronutrient intakes. As in chromosome 1, the linkage evidence for macronutrient intakes was dependent on total food consumption. After adjustment of macronutrient phenotypes for total energy intake, the linkage evidence disappeared [Figure 1 (B, C, and D): dotted lines], which suggested that the QTL influenced total food intake or energy intake rather than specific macronutrients. The region harbored several genes of potential interest for dietary intake phenotypes. However, it would be too speculative and premature to discuss them here.

In the blacks, a promising linkage for carbohydrate and protein intakes was observed on 12q23.3 with a marker in the insulin-like growth factor 1 gene. Some other promising linkages were observed with markers in regions 1q31.3, 1q32.1 and 7q11.1 for

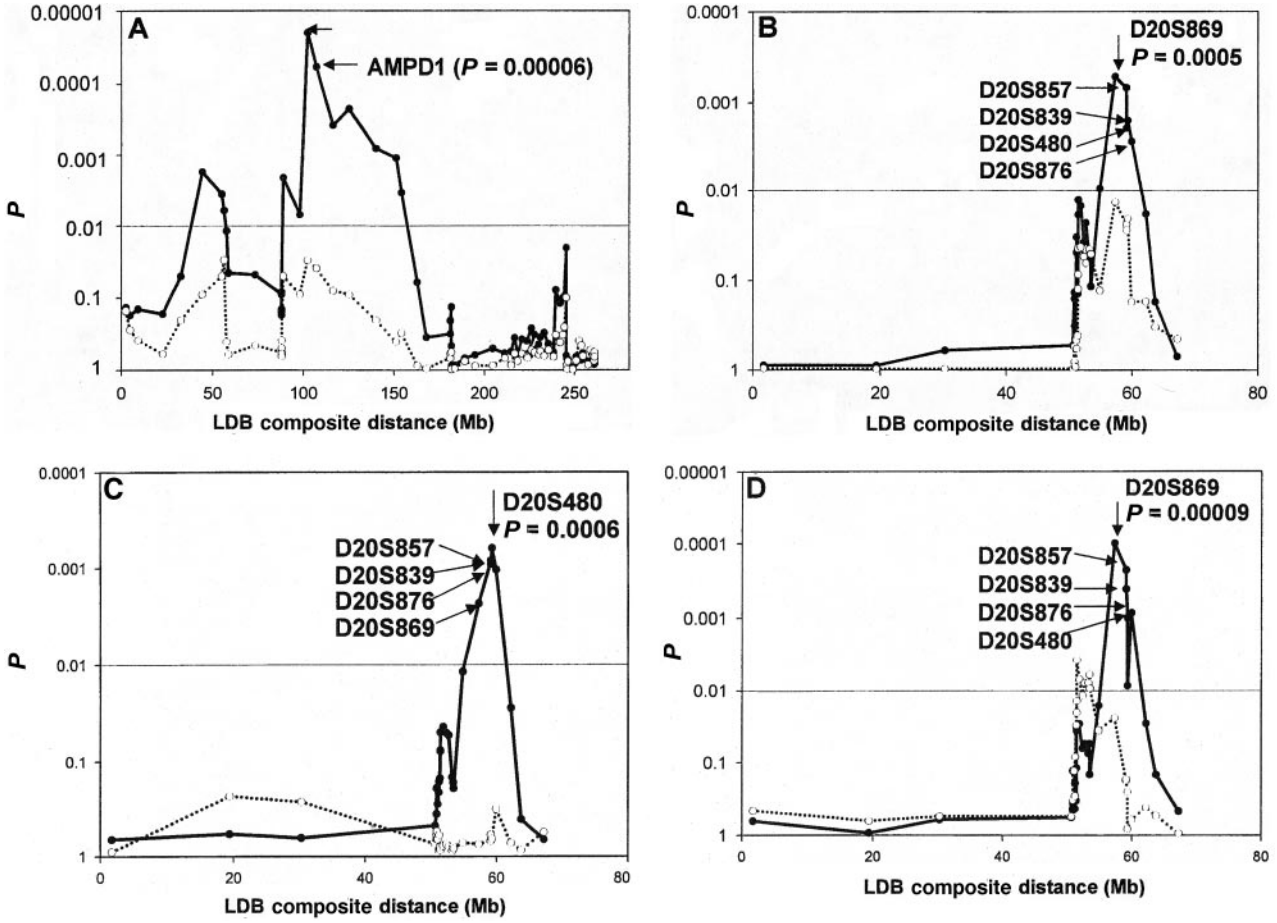

FIGURE 1. Results of multipoint linkage analyses (SIBPAL) in the whites from the Health, Risk Factors, Exercise Training, and Genetics (HERITAGE) Family Study. The lines represent energy nutrient intakes before (solid line) and after (dotted line) adjustment for total energy intake. A: Fat intake on chromosome 1; B: fat intake on chromosome 20; C: carbohydrate intake on chromosome 20; and D: protein intake on chromosome 20. LDB composite distance represents the distance of ordered loci from the *p*-telomere of the chromosome expressed in megabases (Mb) obtained from the Location Data Base (LDB).

protein intake and on 12q24.21 for carbohydrate and fat intake. Sucrose intake was significantly higher in the blacks; promising linkages were observed on 1q43 with marker D1S517 (Table 4). Other promising linkage results for sucrose intake were observed on 6p21.1, which suggests an ethnic difference, because no QTL for sucrose intake was found in the whites.

The present study is the first reported attempt to identify QTLs for dietary energy and energy nutrient intakes in sedentary subjects. Thus, comparison with other studies conducted in humans is not possible. However, Steinle et al (6) recently reported a genome-wide linkage scan for eating behavior–related phenotypes in a cohort of 624 Old Order Amish from 28 families. QTLs for eating restraint, disinhibition, and hunger were found on chromosomes 3, 6, 7, and 16. None of these chromosomal regions overlap with those identified in the present study for energy and energy nutrient intakes. However, the phenotypes were quite different from those of the present study. Steinle et al used 3 eating behavior phenotypes derived from questionnaires: restraint (avoidance of eating), disinhibition (overeating), and hunger. In our study, we evaluated dietary macronutrient intakes and total energy intake from a standardized FFQ. Therefore, the differences in findings between the 2 studies could be primarily related to differences in research design and phenotypes evaluated.

Smith Richards et al (26) recently reported a QTL analysis of self-selected macronutrient diet intake in an F2 population derived from an intercross between C57BL/6J and CAST/EiJ mice. One of the 3 energy-intake QTLs (*kcal3*) was identified on mouse chromosome 2. Approximately 50% of the 1.5 logarithm odds scores CI of (*kcal3*)—73.1, 90 cM on mouse chromosome 2—is syntenic to human chromosome 20p13-q13. The upper limit of the (*kcal3*) CI on the human chromosome 20 is located about 10 million base pairs upstream of our QTL for total energy intake. It is also noteworthy that our chromosome 20 energy-intake QTL is located in the same region where previous studies reported linkages for obesity (27) and type 2 diabetes (28, 29), 2 conditions strongly associated with dietary intake. However, we did not observe any linkages for body composition or fat distribution phenotypes on chromosome 20 in the HERITAGE Family Study cohort (30, 31).

We used a standardized FFQ to assess habitual dietary intake in the HERITAGE Family Study. Although data collection was carefully standardized and monitored and quality-control measures (eg, a central laboratory to score and analyze the questionnaires) were implemented, it should be remembered that all dietary intake assessment instruments based on self-reporting (ie, dietary records, questionnaires, and recall methods) are subject to measurement error. As reviewed (32, 33), all self-reporting

methods tend to underestimate true dietary intake. Recollection of past diets, as in FFQs, may induce random error. Difficulties in methods such as these usually increase the risk of type II error in genetic studies. Thus it is possible that we have missed some QTLs in the current study because of reduced statistical power. At the same time, the QTLs for energy intake detected in the HERITAGE Family Study cohort should be confirmed in other studies.

In summary, significant and suggestive linkages found on 1p12.2, 12q14.1, and 20q13.13 support the hypothesis that genes are likely involved in determining some of the human variation in dietary energy and macronutrient intakes. Most linkages pertained to the intake of total energy rather than to that of specific macronutrients. Dietary intakes represent complex phenotypes that vary greatly among subjects because of local customs, religious beliefs, ethnicity, regional food supply, and the like but that appear to be partly influenced by genetic factors as well.

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