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Evidence of a Novel Quantitative-Trait Locus for Obesity on Chromosome 4p in Mexican Americans

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Although several genomewide scans have identified quantitative-trait loci influencing several obesity-related traits in humans, genes influencing normal variation in obesity phenotypes have not yet been identified. We therefore performed a genome scan of body mass index (BMI) on Mexican Americans, a population prone to obesity and diabetes, using a variance-components linkage analysis to identify loci that influence BMI. We used phenotypic data from 430 individuals (26% diabetics, 59% females, mean age ± SD = 43 ± 17 years, mean BMI ± SD = 30.0 ± 6.7, mean leptin (ng/ml) ± SD = 22.1 ± 17.1) distributed across 27 low-income Mexican American pedigrees who participated in the San Antonio Family Diabetes Study (SAFDS) for whom a 10–15-cM map is available. In this genomewide search, after accounting for the covariate effects of age, sex, diabetes, and leptin, we identified a genetic region exhibiting the most highly significant evidence for linkage (LOD 4.5) with BMI on chromosome 4p (4p15.1) at 42 cM, near marker D4S2912. This linkage result has been confirmed in an independent linkage study of severe obesity in Utah pedigrees. Two strong positional candidates, the human peroxisome proliferator-activated receptor gamma coactivator 1 (*PPARGC1*) and cholecystokinin A receptor *(CCKAR)* with major roles in the development of obesity, are located in this region. In conclusion, we identified a major genetic locus influencing BMI on chromosome 4p in Mexican Americans.

Introduction

Obesity is a complex phenotype resulting from the interaction of both genetic and environmental factors. Obesity is a risk factor for diseases such as type 2 diabetes (T2D), hypertension, and coronary heart disease in all populations, particularly in minority populations in the United States, such as Mexican Americans. Epidemiological studies have indicated that Mexican Americans are prone to complex diseases such as obesity, T2D, dyslipidemia, gallbladder disease, and other metabolic complications (Diehl and Stern 1989; Mitchell et al. 1990; Stern et al. 1990). The Mexican American population is also characterized by increased adiposity and a more centralized distribution of body fat (Joos et al. 1984; Haffner et al. 1986), and it has an increased prevalence of T2D, compared with that among non-Hispanic whites (Stern and Haffner 1990; Haffner et al. 1991).

Several studies have documented that genetic factors are involved in the development of obesity, and ~30%–40% of normal variation is attributable to genetic factors (Bouchard 1997; Barsh et al. 2000; Comuzzie et al. 2001). Epidemiological studies involving twins, adoptees, and families showed that heritability of BMI or body fat varies from ~25% in adoption studies to a high of 70% in twin studies, whereas estimates are ~40% in family studies (Bouchard 1997; Rice et al. 1997; Borecki et al. 1998; Comuzzie and Allison 1998; Hager et al. 1998). Thus, genetic factors play a significant role in establishing an individual's predisposition to developing obesity, whereas environmental and psychological factors contribute significantly to the expression of the obesity phenotype as well (Comuzzie and Allison 1998; Barsh et al. 2000; Kaplan 2000; Comuzzie et al. 2001).

Given the complexity of the obesity phenotype, it has been reported that several important obesity genes may be involved in the regulation of human adipose tissue function and its distribution. Several genes responsible for rare forms of monogenic obesity have been identified in animal models, but only a few of these genes may cause rare forms of monogenic obesity in humans (Barsh et al. 2000). However, despite the fact that knowledge of the genetics of obesity has increased substantially over the past few years, genetic control of common forms of human obesity is poorly understood. To date, on the basis of candidate genes studies and genomewide linkage studies, a number of genes and/or chromosomal

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regions have been reported to be linked or associated with human obesity phenotypes, but causative genes have not yet been identified (Chagnon et al. 2003).

BMI is a commonly used measure of obesity, and it exhibits a complex relationship with T2D and other measures of obesity (e.g., leptin). In view of these complex relationships and interactions between measures of obesity (BMI), leptin, and diabetes, it is hard to identify the trait-specific genes influencing various obesity phenotypes because these phenotypes are under the influence, not only of trait-specific genes, but shared genes (pleiotropic genes) as well (Mahaney et al. 1995; Arya et al. 2001*b*). One way to identify the trait-specific genes is to adjust the given phenotype for the effects of other correlated phenotypes and use the adjusted phenotype in the genetic analysis. Thus, in this study we scanned the genome and performed multipoint linkage analyses to identify the susceptibility loci influencing variation in common forms of obesity represented by the adjusted BMI phenotype in Mexican Americans.

Subjects and Methods

San Antonio Family Diabetes Study

Data were obtained from low-income Mexican American families living in San Antonio, TX, whose members were participants in the San Antonio Family Diabetes Study (SAFDS). Probands for the SAFDS were subjects with T2D identified in a prior epidemiological survey (Stern et al. 1989, 1993). Family members included all first-, second-, and third-degree relatives of probands aged $\geq$18 years. In this study, we used 430 individuals from the 27 largest pedigrees for whom phenotypic and genotypic data were available. An ~10-cM map was used for the multipoint linkage analyses. The Institutional Review Board of the University of Texas Health Science Center at San Antonio approved all procedures, and all subjects gave written informed consent.

Phenotypes

BMI was calculated as weight (in kilograms) divided by height squared (in meters). Leptin levels were measured by a commercial radioimmunoassay (Ma et al. 1996). T2D was diagnosed according to the WHO plasma glucose criteria (World Health Organization 1999). Individuals who reported a history of diabetes and stated that they were receiving insulin or oral antidiabetic agents were also considered to have diabetes. Since SAFDS families were ascertained on type 2 diabetic probands, we corrected for ascertainment bias by conditioning on likelihood of observing the BMI of the proband with T2D in all analyses. In this study, we conducted three types of analyses that differed by the number of covariates included in a given model. The first analysis (BMI1) included age and sex terms as covariates. The second analysis (BMI2) included age and sex terms, and T2D as covariates, and the third analysis (BMI3) included age, sex terms, T2D, and leptin as covariates.

Genotyping of Markers

A total of 439 individuals from the 27 largest SAFDS pedigrees were initially selected for genotyping. DNA was extracted from white blood cells by use of proteinase K digestion/phenol extraction and alcohol precipitation in a semiautomated fashion on an ABI 341 RNA/DNA extractor. Genotypic data were collected mainly by PCR assays with radiolabeled oligonucleotide primers, whereas data for some of the markers were collected using fluorescent dye-labeled primers purchased from Research Genetics. These markers were PCR amplified and loaded onto an Applied Biosystems Model 373 sequencer, and the data were analyzed with Applied Biosystems Genotyper software, as described elsewhere (Duggirala et al. 1999). The details of our genotypic data, including the procedures for checking Mendelian discrepancies, were as described elsewhere (Duggirala et al. 2000). In this study, we used a set of 326 highly polymorphic microsatellite markers, which generated a 10-cM map.

Statistical Genetic Analysis

Multipoint Mapping Procedure

This method uses information on all available markers separated by known map distances and all possible biological relationships simultaneously in deciphering the genetic architecture of a given quantitative phenotype. Since the method requires the distances between the markers to be known, the order of the loci spanning a given chromosome and the likelihood sex-averaged map distances between the loci were obtained employing Kosambi's mapping function using the program CRI-MAP (Green et al. 1990). The advantage of the multipoint approach is that it not only identifies the location of a susceptibility locus but also places CIs on the location parameter, which makes it more powerful than two-point analysis.

Variance Components Linkage Analysis

We used a pedigree-based multipoint variance-components approach to test for linkage between marker loci and the obesity phenotype, using a maximum-likelihood method (Amos 1994; Almasy and Blangero 1998). In this method, the expected genetic covariances between relatives are specified as a function of the IBD relationships at a marker locus, which is assumed to be closely linked to a locus influencing the quantitative trait

in question. The covariance matrix for a pedigree can be written as shown in the following equation:

$$\Omega = \sum_{i=1}^{n} \Pi_i \sigma_{qi}^2 + 2\Phi\sigma_g^2 + \mathbf{I}\sigma_e^2 ,$$

where Ω is the covariance matrix for a given pedigree; Π is a matrix with elements (π_{ijl}) providing the expected proportion of alleles at the specific chromosomal location of the quantitative trait locus that individuals j and l share IBD, which is estimated using genetic marker data; σ_q^2 is the additive genetic variance due to the major locus; Φ is the kinship matrix; σ_g^2 is the variance due to residual additive genetic effects; $\mathbf{I}$ is an identity matrix; and σ_e^2 is the variance due to random environmental effects. Multipoint IBD matrices were estimated using Simwalk2 (Sobel et al. 2001) and were imported into SOLAR (Almasy and Blangero 1998). All multipoint variance-components linkage analyses were performed according to the procedures outlined in SOLAR (Almasy and Blangero 1998).

The null hypothesis that, for a given phenotype, the additive genetic variance due to the QTL, σ_q^2, equals zero (no linkage) can be tested using the likelihood-ratio test. The likelihood of a restricted model, in which σ_q^2 is constrained to 0, is compared with the likelihood of the general model, in which genetic variance due to the QTL (σ_q^2) is estimated. The ln likelihood values of the general model and restricted model are then compared using the likelihood-ratio test. Twice the difference between the ln likelihood values of these models yields a test statistic that is asymptotically distributed as a $\frac{1}{2}:\frac{1}{2}$ mixture of a χ_1^2 and a point mass at 0 (Self and Liang 1987). The likelihood value can be converted into a logarithm (base 10) of odds to obtain a LOD score that is equivalent to the classical LOD score of linkage analysis. A LOD score of $\geq$3.0 was considered to be strong evidence in support of linkage, which is equivalent to a P value of .0001, suggesting that evidence for linkage is 1,000 times greater than the support for no linkage. Other chromosomal regions across the genome with nominal P values of .01 or less (i.e., LOD scores $\geq$1.175) and LOD scores of $\geq$1.9 are considered to show potential linkages and evidence suggestive of linkage, respectively.

Oligogenic Linkage Analysis

We also used a sequential strategy to identify multiple loci affecting the variation in BMI. In this approach, the genome was scanned for linkage and the chromosomal location that yielded the largest marginal LOD score was retained for further conditional analyses. Given the putative location of the first locus, we scanned the genome again and examined the resulting conditional LOD scores. In the two-locus model, the position of the first locus is fixed, and the location of the second locus is allowed to vary through the whole genome. The QTL variance (h_q^2) for the first locus is reestimated along with the second locus. Similarly, in the three-locus model, the positions of the first two loci are fixed, but the effect sizes are reestimated along with the third locus. LOD scores from the oligogenic models can be either joint, if they are compared to the polygenic null model, or conditional, if they are compared to the linkage model containing $n-1$ loci (Blangero and Almasy 1997).

Robust LOD (LOD_R) Score Estimation

To verify our major finding on chromosome 4, we performed simulation analysis. In the simulation analysis, a fully informative marker was simulated that was not linked to the QTL influencing variation in BMI. For this simulated marker, IBD information was calculated, and then linkage analysis was conducted. By use of simulations, the empirical distribution of the LOD scores under the assumption of multivariate normality was determined, on the basis of information obtained from 100,000 replicates by the SOLAR program (Almasy and Blangero 1998). The empirical distribution of the simulated LOD scores was used to assign percentiles to each replicate, and an expected test statistic was calculated on the basis of the percentile. The correction constant was obtained by regressing the expected LOD scores on the observed simulated LOD score, which is used to adjust the observed original LOD scores to obtain robust LOD (LOD_R) scores (Blangero et al. 2001).

Results

Descriptive statistics of the SAFDS subjects used in these analyses are presented in table 1. The patterns of phenotypic, genetic, and environmental correlations (ρ) between trait pairs BMI, leptin, and T2D in Mexican Americans are presented in table 2. The genetic correlations between BMI and leptin and between BMI and T2D were significant ($P < .0001$), whereas the genetic correlation between leptin and T2D was not significant

Table 1

Characteristics of SAFDS Subjects

Variable	Value
Males	41.2%
Females	58.8%
T2D	26.3%
Age, mean ± SD (years)	43.1 ± 17.1
BMI, mean ± SD (kg/m^2)	30.0 ± 6.7[a]
Leptin, mean ± SD (ng/ml):	
Males and Females	22.1 ± 17.1
Males	11.1 ± 7.9
Females	29.7 ± 17.6

[a] Skewness = 0.9; kurtosis = 1.3.

Table 2

Phenotypic (ρ_P), Genetic (ρ_G), and Environmental (ρ_E) Correlations between Phenotype Pairs

Phenotype Pair	Mean Correlation ± SE[a]		
	ρ_P	ρ_G	ρ_E
BMI and leptin	.66 ± .03*	.71 ± .09*	.66 ± .06*
BMI and T2D	.27 ± .07*	.52 ± .23*	.06 ± .16
Leptin and T2D	.00 ± .08	−.03 ± .34	.02 ± .15

Note.—Each trait is adjusted for age and sex terms.
[a] Significant at $P < .0001$.

($P > .05$). Overall, polygenic heritability of BMI was estimated to be 48.6% ± 9.9%, which is highly significant ($P < .0001$), after the effects of age and sex are accounted for (table 3). Given the large sizes of these pedigrees, some related individuals may live in different households. We therefore estimated a household variance component (i.e., household effect was estimated as a surrogate measure of shared environmental influences), which was not significant ($P = .24$).

Following the estimation of heritability, we performed three multipoint univariate linkage analyses across 22 autosomes for BMI. In the first analysis (BMI1), after accounting for the effects of age and sex terms, we found evidence for linkage (LOD 2.1, $P = .0019$) of a genetic region at 39 cM on chromosome 4 near marker D4S2912. In the second analysis (BMI2), after accounting for the covariate effects of age and sex terms and T2D, we again found evidence for linkage (LOD 2.8, $P = .0003$) at the same location. Finally, in the third analysis (BMI3), we removed the effects of leptin in addition to those of age, sex, and T2D. We again found a significant linkage of BMI (LOD 4.5, $P = .000003$) to a nearby genetic location at 42 cM on chromosome 4p, near marker D4S2912. The robust LOD score that corresponds to our maximum observed LOD (4.5) is $LOD_R = 4.1$, $P = .000014$, indicating that type 1 error rates are consistent with asymptotic expectation (i.e., the inflation of type 1 error rate is minimal). Thus, the implicated marker region (at 2 cM centromeric to marker D4S2912) appears to harbor a major susceptibility locus for variation in BMI in Mexican Americans. The LOD scores obtained for BMI from the three analyses were plotted against map positions on chromosome 4, as shown in figure 1. The other chromosomal regions with multipoint LOD scores (>1.175) from only the BMI3 analysis are presented in table 4, and the multipoint LOD profiles across the genome are reported in figure 2.

Since multiple linkage peaks with some evidence for linkage were observed in our genomewide search, we extended variance-components linkage analysis to oligogenic models to incorporate two or more loci simultaneously (Blangero and Almasy 1997; Blangero et al. 1999). As shown in table 5, genetic determinants of BMI3 involve possibly three loci that are found on three different chromosomes. In a joint two-locus analysis, the two-locus model with a LOD score of 6.1 (corresponding to a conditional LOD_R of 1.5 for the second QTL, $P = .009$) accounted for 35% and 23% of variance due to the QTLs on chromosomes 4 (D4S2912) and 11 (D11S1984–D11S988), respectively. The three-locus model with a total LOD score of 7.1 (corresponding to a conditional LOD_R of 0.9 for the third QTL, $P = .03$) accounted for 29%, 20%, and 16% of variance due to the QTLs on chromosomes 4 (D4S2912), 11 (D11S1984–D11S988), and 7 (D7S506–D7S653), respectively. These variance-component estimates for the three-QTL model are likely to be more accurate than those for the simpler models (Blangero and Almasy 1997; Blangero et al. 1999).

Discussion

The association between obesity and T2D has been recognized for decades, and several epidemiological studies have indicated that obesity is a major risk factor for the development of T2D (Kahn and Flier 2000; Nadler and Attie 2001). Although it is clear that obesity influences glucose metabolism through several physiological mechanisms, the cause and effect relationship between obesity and diabetes is still not well understood (Kopelman 2000). Thus, it is often difficult to identify which obese individuals are more likely to become diabetics, since ~80% of individuals with T2D are obese and only 10% of obese individuals may become diabetics (Nadler et al. 2000). On the other hand, the relationship between adiposity (i.e., BMI) and leptin levels has been found to be significant in both men and women of various populations (Maffei et al. 1995; Considine et al. 1996). However, the relationship between leptin and T2D is not clear. Some studies have indicated a complex interrelationship between leptin and insulin resistance (Tritos and

Table 3

BMI Heritability (h^2) in SAFDS Individuals

Phenotype[a]	N	h^2 (%)	Variance Explained by Covariates (%)
BMI1	430	49[b]	6
BMI2	430	48[b]	8
BMI3	386	49[b]	53

[a] BMI1 adjusted for age and sex terms; BMI2 adjusted for age and sex terms and for diabetes; BMI3 adjusted for age and sex terms, diabetes, and leptin.
[b] Significant at $P < .0001$.

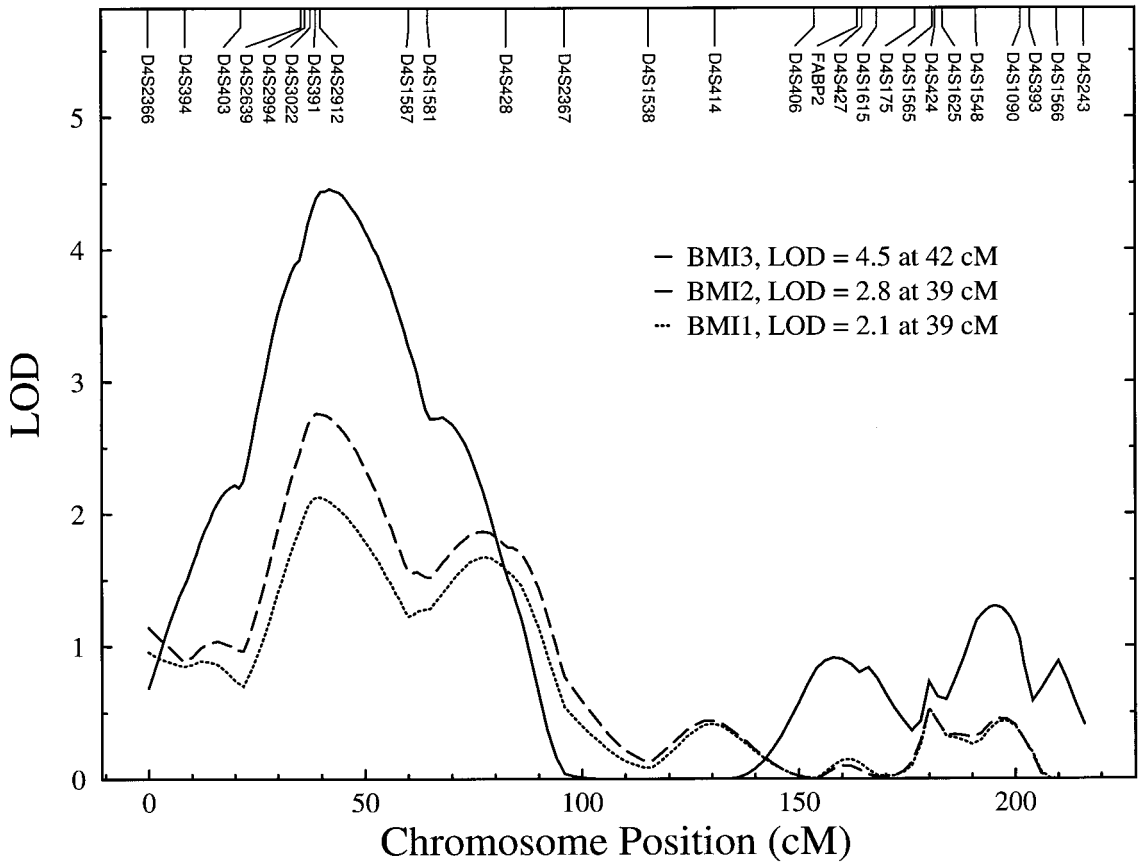

Figure 1 Linkage of BMI to a genetic location on chromosome 4p in Mexican Americans

Mantzoros 1997; Donahue et al. 1999), whereas some have failed to find any association. For example, Haffner et al. (1996) reported no association between leptin levels and diabetic status even though leptin levels are significantly associated with BMI in Mexican Americans. Although there is considerable residual variation in leptin levels at a given BMI value, diabetic status does not account for this variability. In this study, we therefore used the BMI adjusted for the effects of leptin and T2D to identify the genes that influence the common forms of obesity, on the premise that power to localize a trait-specific major gene may be increased by removing some of the background noise due to the phenotypic associations between the correlated traits (Mahaney et al. 1995; Arya et al. 2001*b*).

We analyzed family data collected from Mexican American subjects as part of the San Antonio Family Diabetes Study to identify the trait-specific genes for a single obesity phenotype (i.e., adjusted BMI) in Mexican Americans. As our study reveals, BMI adjusted for the effects of leptin and T2D, which are strong correlates of BMI, is highly and significantly heritable. In addition, our genome scan linkage analysis revealed that there are loci with appreciable influences on BMI. More importantly, this genome scan provided strong evidence for the presence of a novel locus influencing variation in BMI on chromosome 4p. We observed the highest LOD score of 4.5 for BMI3 near marker D4S2912 at 42 cM from pter on chromosome 4p15.1, which provides highly significant support for linkage in a genomewide scan. In fact, the linkage signal (LOD 4.5) was slightly improved after saturation of the region with additional markers between flanking markers D4S2639 and D4S1581, compared with our initial findings (LOD 4.3) in the same region (Arya et al. 2001*a*).

This linkage finding has been replicated in a recent study of severe obesity in women by Stone et al. (2002), who found a highly significant linkage to high BMI in female patients at D4S2632 (4p15.1), with a multipoint heterogeneity LOD of 6.1 and a nonparametric linkage score of 5.3, located ~5 cM telomeric to our region (D4S2912, 4p15.1). Furthermore, this region on chromosome 4p corresponds (~5 cM apart) to the region previously reported to be linked (D4S2397, 4p15.2, LOD 2.3) to abdominal subcutaneous fat in the Quebec family data (Perusse et al. 2001). The region on chro-

Table 4

Chromosomal Regions (LOD ≥1.175, $P \leq .01$) Linked to Obesity Phenotype (BMI3)

Marker Region	Chromosome	Distance from pter, in		LOD Score
		Kosambi cM	Haldane cM	
D2S293–D2S383	2	115	135	2.9
D4S2912	4	36	42	4.5
D4S1548–D4S1090	4	175	195	1.3
D7S506–D7S653	7	90	102	1.9
D9S299–D9S930	9	113	124	2.1
D11S1984–D11S988	11	2	3	2.5
D11S4464	11	150	175	2.3
D18S858–D18S51	18	80	90	1.4

mosome 4p near marker D4S2912 (4p15.1) where we found a significant linkage signal contains two positional candidate genes: peroxisome proliferator activated receptor gamma coactivator 1 (*PPARGC1* [previously called "*PGC-1*"], 4p15.1 [GenBank accession number NT_006316; MIM 604517]) and cholecystokinin A receptor (*CCKAR*, 4p15.1-p15.2 [NT_006316, MIM 118444]) (de Weerth et al. 1993; Huppi et al. 1995).

The gene for PPARGC1 comprises 13 exons spanning a genomic region of ~98 kb and has a cytogenetic location of 4p15.1 (LocusLink). PPARGC1 is a novel transcriptional coactivator that coordinates the activities of many transcriptional factors that play an important role in adaptive thermogenesis (Lowell 1998; Puigserver et al. 1998; Spiegelman et al. 2000), mitochondrial biogenesis (Wu et al. 1999*a*), mitochondrial fatty acid oxidation (Vega et al. 2000), hepatic gluconeogenesis (Herzig et al. 2001; Yoon et al. 2001), and glucose uptake (Michael et al. 2001). PPARGC1 coactivates various nuclear receptors, including PPARγ, and promotes expression of mitochondrial proteins such as UCP1, which plays a major role in thermogenesis, both cold-induced and diet-induced, in brown adipose tissue and skeletal muscle, which is a key component of energy homeostasis and a metabolic defense against obesity (Puigserver et al. 1998; Larrouy et al. 1999).

PPARGC1 increases total cellular respiration and mitochondrial biogenesis through the coactivation of nuclear respiratory factor-1 (NRF-1) (Puigserver et al. 1998; Wu et al. 1999*b*). It promotes mitochondrial biogenesis through its ability to turn on the expression of both NRF-1 and -2 and coactivates NRF-1 through protein-protein interactions (Wu et al. 1999*a*; Monsalve et al. 2000). Both NRF-1 and NRF-2 bind to and regulate the promoters of several genes encoding mitochondrial proteins. Furthermore, it has been shown that expression of *PPARGC-1* is decreased as a function of both insulin resistance and obesity, which in turn leads to decreased expression of NRF-dependent genes and thus to metabolic disturbances such as insulin resistance and diabetes (Patti et al. 2003). Thus, PPARGC1 plays a key role in linking nuclear receptors to the transcriptional program of adaptive thermogenesis, and increasing PPARGC1 activity may be a potential mechanism for energy dissipation and a therapeutic target for weight loss (Puigserver et al. 1998). Recently, Esterbauer et al. (2002) reported that, in middle-aged Austrian women, two *PPARGC1* polymorphisms have been associated significantly with BMI (0.006), with waist (0.01) and hip (0.03) circumferences, and marginally with visceral and subcutaneous fat, suggesting a role of *PPARGC1* in obesity.

Another candidate gene near our peak signal on chromosome 4p is the cholecystokinin A receptor (*CCKAR*), a G protein-coupled 7-transmembrane spanning receptor belonging to the rhodopsin family, which consists of 5 exons covering 9,025 bp with a cytogenetic location at 4p15.1-15.2 (de Weerth et al. 1993; Huppi et al. 1995; Inoue et al. 1997; LocusLink). Both the *PPARGC1* and *CCKAR* genes are thus located centrally on the same physical 22.5 Mb genomic sequence reference contig (NT_006316, accessed September 17, 2003) and are just 2.6 Mb apart, a distance containing at least 26 known or suspected genes. This contig is flanked by markers D4S2912 and D4S1587, which encompass our linkage peak for adjusted BMI (BMI3).

CCKAR plays a role in mediating gallbladder contraction and secretion of pancreatic enzymes. This gene has been implicated in food intake and satiety (Gutzwiller et al. 2000; Beglinger et al. 2001), and *CCKAR* gene promoter polymorphism is associated with body fat (Funakoshi et al. 2000). Although evidence suggests that preabsorptive factors, such as cholecystokinin, are important cofactors in the regulation of energy intake, little is known about the biochemical processes that control hunger and satiety. CCK has been shown to affect the short-term control of food intake in animals and humans, and is proposed to act as a hormonal satiety signal (Drewe et al. 1992; Lieverse et al. 1994; Geary

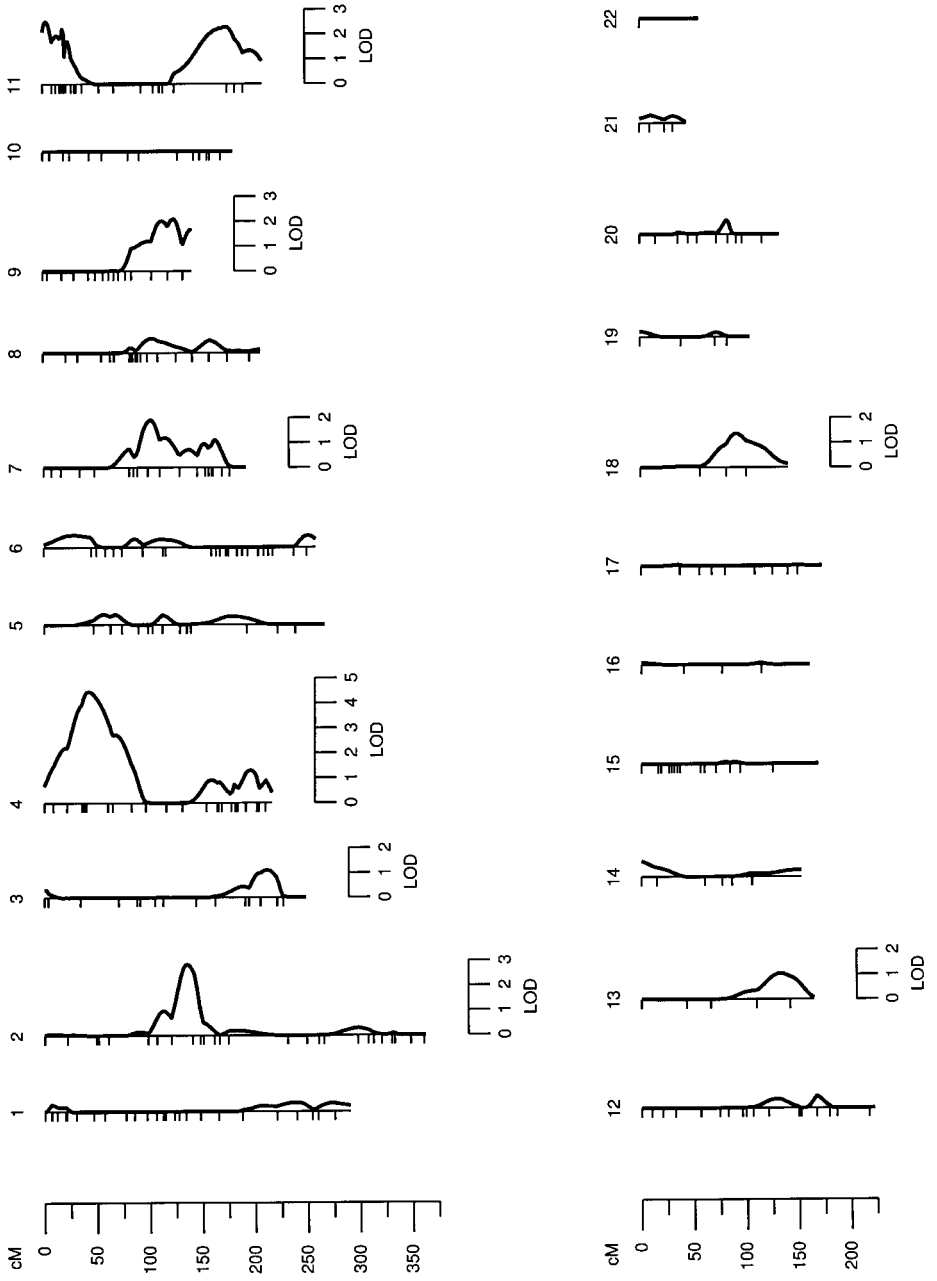

Figure 2 Chromosomal regions linked to BMI in a genome scan (LOD ⩾1.175)

1996; Gutzwiller et al. 1999). For example, fat ingestion stimulates the secretion of a number of gastrointestinal hormones including CCK. In addition, CCK-like peptides are endogenous signals that are mediated by CCK_A receptors, involved in the control of food intake in humans (Gutzwiller et al. 2000). Using a single-strand conformational polymorphism strategy, Inoue et al. (1997) identified five sequence variants, including two missense variants in patients with T2D and obesity, which may be influencing obesity and diabetes. Moran and coworkers (1998) showed that rats that do not express CCK_A receptors develop obesity, hyperglycemia, and T2D.

Several other chromosomal regions across the genome that exhibited some evidence for linkage (LOD >1.175) to BMI correspond with previously reported findings. The genomic region between markers D2S293 and D2S383 (2q12.2-2q14.3) on chromosome 2 (LOD 2.9) corresponds to a previously reported genomic region near markers D2S160 and D2S347 (2q13-2q14.3), which may contain a QTL influencing obesity-related phenotypes in a white population of European origin.

Table 5

Results of the Oligogenic Analysis of Variation in Obesity Phenotype (BMI3)

Model and QTL Region	Chromosome	Location (cM)	Sequential LOD	% of Variation Explained by Locus		
				First	Second	Third
One QTL:						
D4S2912	4	42	4.5	47	…	…
Two QTL:						
D4S2912	4					
D11S1984–D11S988	11	5	6.1	35	23	…
Three QTL:						
D4S2912	4					
D11S1984–D11S988	11					
D7S506–D7S653	7	105	7.1	29	20	16

Other genomic regions on chromosomes 7q and 11q correspond to findings from a number of studies. We have identified a broader region (7q22.1-7q35) on chromosome 7q that contains susceptibility gene(s) for obesity or its related phenotypes—such as extremity skinfolds, BMI, triglyceride, and high-density lipoprotein cholesterol (HDL-C) levels—in Mexican Americans (Duggirala et al. 1996, 2000; Arya et al. 2002). The same region is also implicated by several other studies as influencing BMI in other populations (Wu et al. 2002; Platte et al. 2003). Also, the two genomic regions near markers D11S1984 (11p15.5) and D11S4464 (11q24.1) on chromosome 11 correspond to previously reported genetic regions: a region near markers D11S1984–D11S988 (11p15.5) linked to clinical gallbladder disease (GBD) in Mexican Americans (Duggirala et al. 2003) and a second region, near markers D11S4464–D11S912 (11q24.1), linked to BMI in Pima Indians and other populations (Hanson et al. 1998; Atwood et al. 2002; Adeyemo et al. 2003).

Although ~68 chromosomal regions have been identified as possibly harboring QTLs for human obesity-related phenotypes (Chagnon et al. 2003), specific genes influencing obesity are yet to be identified. Some of the genomic regions hitherto identified to influence obesity-related phenotypes involve chromosomes 2p (Comuzzie et al. 1997; Hager et al. 1998), 6q (Duggirala et al. 2001; Atwood et al. 2002), 7q (Duggirala et al. 1996), 10p (Hager et al. 1998; Hinney et al. 2000), 11q, and 20q (Norman et al. 1998) and have been replicated supporting the presence of genetic variants in these regions that influence the risk of obesity. Thus, genomewide linkage analyses of such obesity-related phenotypes suggest that the observed variation in obesity is attributable to more than one major gene.

Conclusions

Our genome scan results provide strong evidence for a major gene influencing BMI, adjusted for T2D and leptin, on chromosome 4p in Mexican Americans. This linkage was confirmed in an independent study of severe obesity in Utah pedigrees and corresponds with linkage findings from the Quebec Family Study. The implicated genomic region on chromosome 4p contains two strong positional candidate genes, *PPARGC1* and *CCKAR,* which have been shown elsewhere to have a major functional role in the development of obesity. We have begun positional cloning efforts to identify functional variants in these positional candidate genes.

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Electronic-Database Information

Accession numbers and URLs for data presented herein are as follows:

LocusLink, http://www.ncbi.nlm.nih.gov/LocusLink/ (NCBI Build 33, assembled from Genbank genomic sequence data on April 28, 2003)

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for *PPARGC1* and *CCKAR*)

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Erratum

Because of a clerical error, incorrect "received" dates were printed for manuscripts published in the December 2003 and February 2004 issues of the *Journal*. The corrected dates are as follows:

The article entitled "*MDR1* Ala893 Polymorphism Is Associated with Inflammatory Bowel Disease," by Brant et al. (73:1282–1292), was received May 30, 2003.

The article entitled "Genomewide Linkage Analysis for Internal Carotid Artery Intimal Medial Thickness: Evidence for Linkage to Chromosome 12," by Fox et al. (74:253–261), was received April 16, 2003.

The article entitled "Premature Myocardial Infarction Novel Susceptibility Locus on Chromosome 1P34-36 Identified by Genomewide Linkage Analysis," by Wang et al. (74:262–271), was received July 31, 2003.

The article entitled "Evidence of a Novel Quantitative-Trait Locus for Obesity on Chromosome 4p in Mexican Americans," by Arya et al. (74:272–282), was received September 12, 2003.

The report entitled "Mutations in the *VLGR1* Gene Implicate G-Protein Signaling in the Pathogenesis of Usher Syndrome Type II," by Weston et al. (74:357–366), was received October 16, 2003.

The *Journal* regrets these errors.