Am. J. Hum. Genet. 63:831–838, 1998

Evidence for at Least Two Major Loci Influencing Human Fatness

Ingrid B. Borecki,[1] John Blangero,[3] Treva Rice,[1] Louis Pérusse,[4] Claude Bouchard,[4] and D. C. Rao[1,2]

[1]Division of Biostatistics and [2]Departments of Psychiatry and Genetics, Washington University School of Medicine, St. Louis; [3]Department of Genetics, Southwest Foundation for Biomedical Research, San Antonio; and [4]Physical Activity Sciences Laboratory, Laval University, Ste-Foy, Quebec

Summary

The genetics of human fatness has been the subject of many recent studies, motivated by the increased morbidity and mortality associated with obesity, as well as the increasing prevalence of overweight and obesity. The body-mass index (BMI) and fat mass (FM), measured by underwater weighing, were assessed for 1,630 individuals from ~300 families from phase 1 of the Quebec Family Study. The two phenotypes are highly correlated (~.8) in adults, and previous segregation analysis revealed evidence for a recessive major gene for each trait. In our study, we utilized bivariate segregation analysis to determine the source(s) of phenotypic correlation—namely, a pleiotropic major gene, shared familial factors/polygenes, or shared nontransmitted environmental factors. Analysis was performed by use of the Pedigree Analysis Package, with extensions to the bivariate case. Tests of hypotheses provided evidence for *two* pleiotropic recessive loci, together accounting for 64% and 47% of the variance in BMI and FM, respectively. Under the model, all sources of phenotypic correlation were significant: 73% of the covariance was attributed to the pleiotropic major loci, 8% to residual familial effects, and 19% to nontransmitted environmental factors. The high degree of genetic identity between the two traits is not surprising, since the BMI often is used as a surrogate for FM; however, simultaneous analysis of both phenotypes enabled the detection of a second major locus, which apparently does not affect extreme overweight (as does the primary major locus) but which affects variation in the "normal" range.

Received January 20, 1998; accepted for publication June 26, 1998; electronically published August 14, 1998.

Address for correspondence and reprints: Dr. Ingrid B. Borecki, Division of Biostatistics, Washington University School of Medicine, Box 8067, 660 South Euclid Avenue, St. Louis, MO 63110. E-mail: ingrid@wubios.wustl.edu

0002-9297/98/6303-0025$02.00

Introduction

The genetics of human fatness has been the subject of many recent genetic epidemiological studies, motivated by the increased morbidity and mortality associated with obesity (Garrison et al. 1996), as well as the increasing prevalence of overweight persons in many countries and societies all over the world (Price 1992; Popkin et al. 1995). The realization that the development of obesity probably is influenced by genetic factors has spurred efforts to identify predisposing genes that also may account for observed familial resemblance for fatness. Significant progress has been made in the characterization of familial patterns of inheritance for measures of absolute amount of fat (Rice et al. 1993*b;* Comuzzie et al. 1995) and relative fat patterns (Hasstedt et al. 1989; Borecki et al. 1995), specifically, those for abdominal visceral fat (Bouchard et al. 1996; Rice et al. 1997*a*, 1997*b*); all of these phenotypes are associated with insulin resistance, dyslipidemias, and increased risk of coronary heart disease.

One of the most extensively studied obesity-related phenotypes is the body-mass index (BMI). Calculated as weight (in kilograms) divided by height (in meters) squared, the BMI was devised as a surrogate measure of the amount of body fat. In fact, these phenotypes are highly correlated (~.8) in adults, and correlation is ~.6 among adolescents: the lower correlation among younger people most likely is attributable to the pronounced age-dependent developmental effects on fatness and the relative fat distribution observed during maturation (Borecki et al. 1991). Evidence from several family studies has supported a major-gene hypothesis for BMI (Price et al. 1990; Province et al. 1990; Moll et al. 1991; Borecki et al. 1993). These results have been remarkably consistent, indicating recessive inheritance of a major gene with a susceptibility-allele frequency of ~20%–30%. This result was surprising not only in view of the expected complexity of the underlying etiologic mechanism, but also vis-à-vis the heterogeneity of the BMI, which, more accurately, is an index of heaviness rather than fatness, since it reflects the combined effects of fat mass and lean mass (Bouchard and Pérusse 1988).

Table 1

Descriptive Statistics for the Raw Phenotypes

	BMI		FM	
FAMILY GROUP	Mean [SD] (kg/m^2)	No. of Subjects	Mean [SD] (kg)	No. of Subjects
Fathers	25.4 [3.3]	357	18.2 [7.2]	205
Mothers	23.4 [3.6]	368	19.0 [6.2]	189
Sons	19.2 [2.8]	484	6.5 [4.0]	288
Daughters	19.1 [2.8]	419	9.7 [4.7]	265

Despite the fact that these results represent perhaps the most consistently replicated statistical evidence for a major locus, the gene(s) underlying trait variability remains unidentified.

Meanwhile, fat mass (FM) has been measured in two family studies of significant size: the Quebec Family Study (QFS) of French Canadians, which used underwater weighing, and the San Antonio Family Heart Study of Mexican Americans, which used bioelectric impedance. Rice et al. (1993*b*) and Comuzzie et al. (1995) reported evidence of a recessive major gene that accounted for ~45% and ~40% of the variation in FM, respectively, although, interestingly, the effect of the major locus was found to depend on sex, in the Mexican Americans. The gene frequencies were estimated to be 30% and 25%, respectively. These parameter estimates were very reminiscent of those observed for BMI. In contrast, a recent study by Lecomte et al. (1997) did not infer a major gene for FM (also measured by bioelectrical impedance): although the major-gene hypothesis fit the data better than a simple multifactorial model did, Mendelian transmission could not be demonstrated, despite allowance for possible interactions of the putative gene with age and sex. However, Lecomte et al. (1997) note that their results do not preclude the existence of several genes acting in a more complex manner.

The QFS is a well-established ongoing study of fatness, in which an extensive array of measurements have been performed on study participants. Both BMI and FM have been analyzed extensively. As already mentioned, data from this study support a recessive–major-gene hypothesis for BMI (Borecki et al. 1993; Rice et al. 1993*a*) as well as for FM (Rice et al. 1993*b*). The major genes detected by segregation analysis accounted for 40% and 45% of the variance in BMI and FM, respectively, with an additional 42% and 22% of the variance attributable to other genetic or familial factors (the so-called multifactorial component) for each trait. Given that BMI is a heterogeneous phenotype resulting from the combined effects of fat, muscle, bone, and organ mass, it is of interest to investigate whether the major locus detected for FM is actually the same locus as that detected in the analysis of BMI and whether other sources of phenotypic variation are common to both traits. Although a relevant correlational study of these data has suggested a common familial basis for percent body fat and BMI (Rice et al. 1995), we undertook, in our study, a full bivariate segregation analysis of the two traits, to identify the sources of phenotypic correlation and to partition the phenotypic covariance.

Subjects and Methods

The Quebec Family Study

Phase 1 of the QFS consisted of 1,630 individuals from randomly sampled French Canadian families living in the Quebec City area and recruited through the media (i.e., local and regional newspapers, radio, TV, and flyers distributed to churches and schools), during the years 1978–81, for the study of the genetic effects on several physiological and biochemical traits. The sample appears to be representative of the general population (Pérusse et al. 1989). The study protocol was reviewed and approved by the Institutional Review Board of Laval University, and written informed consent was obtained from all adults; for minors, the written consent of the minor and of his/her parents was obtained. The age ranges were 30–60 years for parents and 8–26 years for offspring. Participants were required to be in good health, and certain exclusions were made for the purposes of this analysis. First, adopted offspring with no genetic relationship to either of the parents, as well as cousins and friends living with the family, were excluded. Couples with no offspring also were excluded. One twin was excluded at random from each of six monozygotic twin pairs, although verified dizygotic twin pairs were retained. In all, there remained 301 nuclear families, with 282 fathers, 294 mothers, and 647 offspring.

Descriptive statistics of the distributions of raw BMI and FM values for all participants in the QFS at phase I are shown in table 1. As can be seen from these figures, individuals from this population tend to be somewhat leaner than those from other published populations, with fewer extremely overweight individuals. The raw phenotypes were adjusted prior to analysis, by multiple regression, for the effects of age and its higher-order terms on the mean and variance within generation/sex groups (Borecki et al. 1991); there was minimal heteroscedasticity. Finally, the residual phenotypes were standardized to a mean of 0 and an SD of 1, within the four groups. This adjustment procedure was undertaken to remove the aggregate effects of age and sex on the phenotypic variation.

Segregation-Analysis Methodology

Segregation analysis was performed by use of the Pedigree Analysis Package, version 3.0 (Hasstedt 1989), by means of extensions to the bivariate case, provided by

Blangero and Konigsberg (1991). This is basically a mixed-model formulation in which each phenotype is assumed to be potentially influenced by the independent and additive contributions of a major gene (g), a polygenic/multifactorial background (G), and a nontransmitted environmental residual (E). Consider two traits, denoted "1" and "2," and two genes, denoted "A" and "B." It is assumed that loci A and B are independent; that is, they are not linked, and there is no incidental disequilibrium between them (fig. 1). Three possible sources of phenotypic correlation are modeled. The first is due to the pleiotropic effect of either locus or of both major loci affecting each trait. The second is due to a correlation between the relevant polygenic components for each trait (i.e., between G_1 and G_2), and the third is due to a correlation between the relevant nontransmitted environmental factors for each trait (i.e., between E_1 and E_2).

The parameters of the model are listed in table 2. Each locus has two alleles (A and a or B and b), for which the uppercase alleles are associated with lower trait values and the frequencies are described by p,—that is, p(A) and p(B). Both locus A and locus B potentially influence each trait (A_1 and A_2 or B_1 and B_2, respectively). By use of classic biometric parameterization, the effects of each locus can be partitioned into the additive effects (a) and the dominance effects (d) that produce deviations from the grand mean for each trait (m_1 and m_2) in the population. For our study, we assumed that there were no interactions (i.e., $a \times a$, $d \times d$, and $a \times d$ each equal zero). The residual SD for each trait also can be estimated, after accounting for any effects of one or both major loci. The proportion of the residual variance attributable to polygenic effects is the heritability, h^2. The correlation between the polygenic components is r_G, and the correlation between the nontransmitted environmental components is r_E.

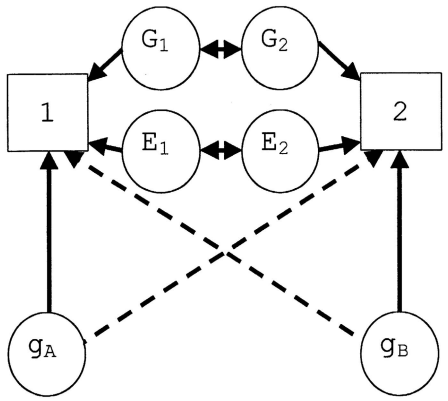


Figure 1 Bivariate segregation model, including unmeasured etiologic factors (represented by circles). g = a major locus, G = a multifactorial/polygenic component, and E = a nontransmitted environmental residual. Each of these factors potentially affect the measured phenotypes (represented by squares). Trait 1 is BMI, and trait 2 is FM. Single-headed arrows indicate the assumed direction of causation, and double-headed arrows indicate correlation.

Table 2

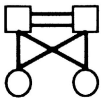
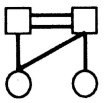
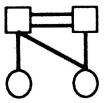
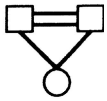
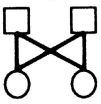
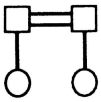
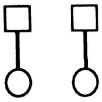
Parameters of the Bivariate Model

Parameter	Description
p(A)	Frequency of allele A
p(B)	Frequency of allele B
Trait 1:	
m_1	Population mean
$a(A)_1$	Additive genetic effect of locus A
$a(B)_1$	Additive genetic effect of locus B
$d(A)_1$	Dominance effect of locus A
$d(B)_1$	Dominance effect of locus B
SD_1	Residual SD
h_1^2	Proportion of residual variance due to polygenes
Trait 2:	
m_2	Population mean
$a(A)_2$	Additive genetic effect of locus A
$a(B)_2$	Additive genetic effect of locus B
$d(A)_2$	Dominance effect of locus A
$d(B)_2$	Dominance effect of locus B
SD_2	Residual SD
h_2^2	Proportion of residual variance due to polygenes
r_G	Correlation between multifactorial/polygenic components, for traits 1 and 2
r_E	Correlation between nontransmitted environmental components, for traits 1 and 2

The parameter estimates from a two-locus model can be used to compute certain other quantities of interest. Two-locus genotype means can be computed as the sum of the overall phenotypic mean and the relevant additive and dominance contributions of the constituent alleles. The marginal single-locus genotype means can be obtained by conditioning on the genotype at the alternative locus. The variance is decomposed in the usual way. Details are described in the article by Blangero et al. (1990).

The parameters of the model are estimated by the maximum-likelihood method, and tests of hypotheses are performed by use of likelihood-ratio tests. The main hypotheses of interest are outlined in figure 2, in which we show, specifically, which parameters are estimated and which are constrained to 0 in order to form the relevant null hypotheses.

Since a complete univariate segregation analysis of each phenotype already had been performed (Borecki et al. 1993; Rice et al. 1993*b*), we were no longer interested in testing the basic features of the models; that is, we accepted that there is evidence for a Mendelian major locus with a residual multifactorial component, for each trait. Rather, we were interested in characterizing the phenotypic correlation between the two traits. Previous analyses of these data suggested the presence of a genotype-by-covariate interaction, and Mendelian segre-

Model	Hypothesis	Estimated parameters	Fixed parameters	N_e	
I	full 2-locus, general model	p(A), p(B), m_1, aA1, aB1, dA1, dB1, SD_1, h^2_1, m_2, aA2, aB2, dA2, dB2, SD_2, h^2_2, r_G, r_E	interactions terms, covariates, at zero (assumed throughout)	18	
II	no effect of locus B on trait 1 (pleiotropic locus with trait 2 having its own locus)	p(A), p(B), m_1, aA1, dA1, SD_1, h^2_1, m_2, aA2, aB2, dA2, dB2, SD_2, h^2_2, r_G, r_E	aB1 = dB1 = 0	16	
III	no effect of locus A on trait 2 (pleiotropic locus with trait 1 having its own locus)	p(A), p(B), m_1, aA1, aB1, dA1, dB1, SD_1, h^2_1, m_2, aB2, dB2, SD_2, h^2_2, r_G, r_E	aA2 = dA2 = 0	16	
IV	no effect of a 2nd locus (only one pleiotropic gene)	p(A), m_1, aA1, dA1, SD_1, h^2_1, m_2, aA2, dA2, SD_2, h^2_2, r_G, r_E	p(B) = aB1 = dB1 = aB2 = dB2 = 0	13	
V	no polygenic or environmental residual correlations	p(A), p(B), m_1, aA1, aB1, dA1, dB1, SD_1, h^2_1, m_2, aA2, aB2, dA2, dB2, SD_2, h^2_2	$r_G = r_E = 0$	16	
VI	no major gene pleiotropy (each trait with its own gene)	p(A), p(B), m_1, aA1, dA1, SD_1, h^2_1, m_2, aB2, dB2, SD_2, h^2_2, r_G, r_E	aB1 = dB1 = aA2 = dA2 = 0	14	
VII	no phenotypic correlation (joint univariates)	p(A), p(B), m_1, aA1, dA1, SD_1, h^2_1, m_2, aB2, dB2, SD_2, h^2_2	aB1 = dB1 = aA2 = dA2 = 0 $r_G = r_E = 0$	12	

N_e is the number of estimated parameters

Figure 2 Main hypotheses under the bivariate model

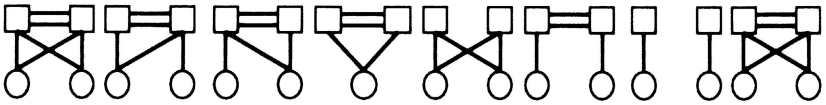
gation ratios for the putative BMI locus were rejected (Rice et al. 1993*a*) until genotype-specific age and sex effects were modeled (Borecki et al. 1993). In short, the effect of the major locus was greater in women than in men and decreased over time. However, the characterization of the major gene was substantially unchanged from that observed when no covariates were modeled. Furthermore, there were no significant genotype-specific effects for FM. For these reasons, we did not include these effects in our study, since the focus was on the sources of phenotypic correlation.

A systematic evaluation of all the possible sources of phenotypic covariance was undertaken, by comparison with a full model including all parameters (fig. 2, model I). We progressively dropped one effect at a time, until there were no sources of phenotypic correlation in the model (fig. 2, model VII) and the model was simply the two univariate solutions for each trait.

Akaike's information criterion (AIC) also is a useful measure in the evaluation of the relative fit of non-nested models or in identification of parsimonious models (Akaike 1974). AIC values are calculated simply as minus twice the log likelihood of the model, plus twice the number of estimated parameters in that model. The model with the *lowest* AIC value is the most parsimonious and provides the best relative fit to the data.

Results

The results of the model fitting are displayed in figure 3; in this figure, trait 1 is BMI, and trait 2 is FM. As compared with the general model allowing for all sources of phenotypic correlation (model I), as described in Subjects and Methods, the model in which locus B does not have a pleiotropic effect on trait 1 (model II) was rejected ($\chi^2_2 = 26.02$, $P < .0001$). Likewise, the null hypothesis that locus A does not have a pleiotropic effect on trait 2 (model III) was rejected ($\chi^2_2 = 23.28$, $P < .0001$). Allowing for only one pleiotropic locus (model IV) was rejected, when compared with the more general alternative of two pleiotropic loci ($\chi^2_5 = 32.16$, $P < .0001$). Two pleiotropic loci without residual multifactorial and environmental correlations (model V) was rejected ($\chi^2_2 = 43.88$, $P < .0001$). Alternatively, allowing all of the phenotypic correlation to be absorbed by correlated multifactorial and environmental components, while accounting for independent and respective major-locus effects (model VI), likewise was rejected ($\chi^2_4 =$



Model[1] →	I	II	III	IV	V	VI	VII	I′
p(A)	.807	.735	.793	.738	.784	.776	.731	.796
p(B)	.534	.278	.717	0	.532	.706	.710	.528
m_1	2.020	1.141	1.664	1.144	2.260	.724	1.127	1.874
aA1	1.596	1.254	.731	1.248	1.929	.761	1.243	1.560
aB1	.666	0	1.168	0	.536	0	0	.734
dA1	1.637	1.343	.656	1.356	1.293	.807	1.330	=aA1
dB1	.902	0	1.197	0	1.193	0	0	=aB1
SD	.647	.848	.769	.850	.520	.979	.844	.650
h^2	.435	.449	.415	.459	.528	.374	.463	.377
m_2	1.610	1.365	.887	.976	1.848	.455	.916	1.575
aA2	1.508	1.242	0	1.250	1.744	0	0	1.390
aB2	.524	-.601	1.254	0	.432	.663	1.200	.521
dA2	1.133	.970	0	.975	.868	0	0	=aA2
dB2	.575	.328	.836	0	.964	.445	.990	=aB2
SD	.728	.739	.749	.808	.573	.935	.786	.745
h^2	.341	.266	.277	.355	.456	.386	.380	.390
r_G	.396	.695	.502	.580	0	.781	0	.351
r_E	.547	.661	.688	.646	0	.824	0	.529
-2lnLK[2]	0.00	26.02	23.28	32.16	43.88	97.55	480.66	5.42
# parameters estimated	18	16	16	13	16	14	12	14
χ^2	-	26.02	23.28	32.16	43.88	97.55	480.66	5.42
df	-	2	2	5	2	4	6	4
P	-	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	.247

[1] The specific models are described in table 2; here, model I′ differs from I in that all major gene effects are modeled to follow a recessive pattern of inheritance.
[2] Minus twice the log-likelihood, scaled

Figure 3 Bivariate segregation analysis of BMI (trait 1) and FM (trait 2)

97.55, $P < .0001$). Finally, since BMI and FM are highly correlated, it is not surprising that a model that posits no correlation between the phenotypes (model VII) was rejected vigorously ($\chi^2_6 = 480.66$, $P < .0001$). Therefore, the general model, which allows for two pleiotropic major loci and for correlations of the multifactorial and environmental components, can be inferred. Although our original hypothesis—namely, that the BMI and FM loci are one and the same—was supported by this analysis, the evidence for a *second* locus that also is pleiotropic with respect to both traits was surprising. An additional test of the dominance parameters indicated that both loci appear to segregate in a recessive fashion, with respect to both BMI and FM (model I′; $\chi^2_4 = 5.42$, $P = .25$).

The proportion of variance in each phenotype attributable to each factor included in the inferred model (I′) is displayed in table 3. Together, the two loci accounted for 64% and 47% of the variance in BMI and FM, respectively, with locus A accounting for slightly more than half this total. There remains additional multifactorial heritability in each case, accounting for 13% and 21% of the variance in BMI and FM, respectively. Data for the variance decomposition obtained from the single-locus, univariate analysis also are given in table 3. Interestingly, the parameterization of the second locus increased the variance attributable to major loci, from 40% to 64%, with a corresponding decrease in the residual multifactorial variance, from 42% to 13%, for BMI. In contrast, the relative variance decomposition for FM remained fairly stable, with the major-locus variance essentially being split between the two loci.

The marginal means for each of the putative loci are shown in table 4. The frequency of the recessive genotype for locus A, which is associated with higher values for BMI and FM, is similar to that found in the uni-

Table 3

Partitioning of the Variances

Phenotype and Type of Analysis	Variance (%)		
	Major Loci [Locus A/Locus B]	Multifactorial Component	Residual Component
BMI:			
Bivariate	64 [33/32]	13	22
Univariate	40	42	18
FM:			
Bivariate	47 [29/18]	21	32
Univariate	45	22	33

variate analyses of these same data, whereas the marginal effect of locus B appeared to be more modest, affecting variation in the "normal" range. Although the effect of locus A is greater than that of locus B, in terms of the displacement between genotypic means for both traits, the greater frequency of the recessive allele at locus B accounts for the roughly similar magnitude of effect of the two loci. Note that it is assumed the two loci act additively, such that the lowest mean was seen for the joint genotype A-B- (BMI −0.383; FM −0.324) and the highest mean was associated with genotype aabb (BMI 4.205; FM 3.498). Therefore, double-homozygous individuals are extremely overweight, with mean BMI values of ~4.2 SD above the population mean (~39.3 kg/m^2 for adult men and ~38.5 kg/m^2 for adult women, in this sample).

The correlation between BMI and FM in these data is .82, on the basis of the estimated total phenotypic covariance matrix. The total covariance between the two traits can be partitioned into the model components: 73% was due to the two pleiotropic major loci (41% attributable to locus A and 32% to locus B), 8% was due to other shared or common familial factors, and 19% was due to shared or common environmental factors nontransmitted in families. These figures imply a high degree of genetic identity between BMI and FM.

Discussion

The present study was undertaken to investigate the common genetic architecture of the BMI and FM. Since major loci and residual familial factors had been detected for each phenotype individually, we hypothesized that some of these etiologic factors may be common to both traits, given their high correlation. The results suggest a high degree of genetic identity between the two traits: 81% of the total estimated covariance was familial, and 90% of the familial component of the covariance was accounted for by two major loci. These results suggest a high degree of genetic pleiotropy. However, in this context, pleiotropy perhaps is somewhat different from the traditional concept, since the two phenotypes analyzed in our study are often used, in fieldwork and clinical research, as alternative measurements of the same underlying quantity of interest. Presumably, the genes detected in our study act in the same way and on the same targets, so as to affect similarly the observed BMI and FM. However, the two phenotypes have different residuals that reflect different levels of measurement error, as well as the effect of other genes and/or factors relevant to the lean-mass component of the BMI. In this sense, FM is a cleaner and more informative phenotype for genetic studies. Nonetheless, despite the fact that the BMI is only a surrogate measure of FM, it appears to be influenced by some of the same genetic factors and is, therefore, also a useful phenotype for genetic analysis.

There is growing evidence that genes with relatively large effects influence human body mass and body fat. Segregation analyses of family data on both BMI and FM have provided consistent evidence of major loci. Moreover, direct evidence of such effects has been accumulating, owing to the increased effort to map obesity genes. For example, by using highly informative families and markers, Comuzzie et al. (1997) recently identified a putative obesity-susceptibility gene, on 2p, affecting both serum-leptin levels and total FM. The locus, identified by linkage analysis, accounted for ~32% (±10%) of the variance in FM, which is just slightly lower than the major-locus variance of 40% estimated from univariate segregation analysis. This locus possibly is one of the two detected in our study, and a linkage analysis to evaluate this hypothesis is underway.

A couple of other recent studies also addressed an oligogenic hypothesis for fatness phenotypes. Hasstedt et al. (1997; the Utah study) investigated the genetic factors influencing BMI in pedigrees ascertained through a pair of siblings affected with non–insulin-dependent diabetes mellitus (NIDDM). Using segregation analysis and sequential tests, they reported evidence for two recessive loci, one influencing "extreme" obesity and the other influencing "moderate" obesity. The results are highly comparable: Hasstedt et al. (1997) found that the two recessive loci accounted for 68% of the variance in BMI; we found that the loci accounted for 64%. Although they found no residual familial effects, after accounting for the major loci, we found in our data a modest residual heritability of 13%. The estimated characteristics of the major loci also showed a great deal of similarity: the recessive-allele frequency and displacement for the locus associated with "extreme" obesity (28% and 4.47 within-distribution SD units [Utah study] vs. 19% and 4.80 SD [our study]) and those for the locus associated with "moderate" obesity (42% and 2.20 SD [Utah study] vs. 47% and 2.30 SD [our study]) were quite comparable.

The minor variations between the two studies could

Table 4

Marginal Genotype-Specific Means

Phenotype and Type of Analysis	Marginal Mean					
	Locus A Genotype (Frequency)			Locus B Genotype (Frequency)		
	AA (.63)	Aa (.32)	aa (.04)	BB (.28)	Bb (.50)	bb (.22)
BMI:						
Bivariate	−.093	=AA	3.027	−.290	=BB	1.178
Univariate	−.151	=AA	2.399	…	…	…
FM:						
Bivariate	−.104	=AA	2.676	−.220	=BB	.822
Univariate	−.185	=AA	2.087	…	…	…

have been influenced by the fact that the pedigrees in the Utah study were ascertained for familial NIDDM, which could have resulted in a greater representation of obese individuals and a tendency for underestimation of familial effects, as seen in the data discussed above. In contrast, our study utilized a sample of families with individuals who tended to be leaner than those from other populations. Finally, the subjects in the Utah study were adults, whereas our study also included children 8–26 years of age. Despite these differences, the results from the two studies are remarkably consistent. Hasstedt et al. (1997) raised the question of whether the major loci detected in the Utah study produce both NIDDM and obesity pleiotropically or whether they produce obesity only. Although the results from our study do not answer this question unequivocally, we found that, if indeed we detected the same major loci, the loci also had pleiotropic effects on fat mass, per se, and not necessarily on NIDDM, since known diabetics were excluded from our sample.

Another recent study, involving the National Heart, Lung, and Blood Institute Family Heart Study, examined BMI in a random sample of families (Borecki et al. 1998); all subjects were adults $\geqslant 25$ years of age. Single-locus segregation analysis revealed evidence for a recessive major gene, comparable to the results of the previous studies cited above; however, an alternative maximum-likelihood solution strongly suggested the presence of a second major factor, largely accounting for cases of extreme obesity. Although the transmission of the second factor could not be readily shown to follow Mendelian proportions, the presence of two loci, as was detected in our study, possibly could explain that pattern of results, with extremely obese individuals being double homozygotes. In fact, this hypothesis was suggested by the results of an earlier study, by Price et al. (1990). Although their segregation analysis supported the presence of a recessive major gene, commingling analysis actually supported a three-component solution with a rare component associated with extremely obese subjects, whose level of adiposity is comparable to that of our double homozygotes, and an intermediate component representing ~6% of the sample, comparable to the recessive homozygous genotype most often detected by many previous univariate segregation analyses (Price et al. 1990; Province et al. 1990; Moll et al. 1991; Borecki et al. 1993, 1998). This latter component is also comparable to the recessive homozygous genotype for locus A in our study and to the locus for "extreme" obesity in the Utah study (Hasstedt et al. 1997).

It should be noted that the model employed in our analyses has only two major loci. The potential for other loci was not tested explicitly, except as a residual genetic heritability. Therefore, these results do not exclude the possibility of other loci. However, the observations that Hasstedt et al. (1997) found no residual heritability after accounting for the effects of the two loci and that we found rather modest residual heritabilities (13% for BMI and 21% for FM) suggest that the effects of any remaining loci are likely to be small in comparison. Nonetheless, the results of our analysis suggest that there may be at least two loci with effects that are large enough that the prospect of mapping these loci is quite good.

There are a number of interesting candidate genes that could be considered for fatness genes. Hasstedt et al. (1997) did not find evidence of linkage to nine candidates, including the Prader-Willi chromosomal region, the human homologue of the mouse agouti gene, and the genes for leptin, the leptin receptor, the β_3-adrenergic receptor, lipoprotein lipase, hepatic lipase, glycogen synthase, and tumor necrosis factor α. However, results from two studies searching for loci influencing fatness, by means of genomic scans, have identified candidate regions on 2p (Comuzzie et al. 1997) and on 11q and 3p (Norman et al. 1997). Other possibilities are reviewed in the article by Chagnon et al. (1998). In any case, the results from our study strongly suggest that there are at least two loci affecting body mass and body fat that have a relatively large phenotypic effect, suggesting that they may be relatively easy to find. Other loci that may account for the residual familiality are likely to have much smaller, subtle effects.

Acknowledgments

This work was supported, in part, by National Institutes of Health grants GM28719 and HD18281 and by Medical Research Council of Canada grants MT13960 and PG11811.

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