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The Genetic and Environmental Sources of Body Mass Index Variability: The Muscatine Ponderosity Family Study

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Summary

The role of genetic and environmental factors in determining the variability in body mass index (BMI; kg/m^2) was investigated in 1,302 relatives identified through 284 schoolchildren from Muscatine, IA. BMI levels were first adjusted for variability in age, by gender and by relative type. There was significant familial aggregation of adjusted BMI in the pedigrees, as indicated by inter- and intraclass correlation coefficients significantly different from zero. A mixture of two normal distributions fit the adjusted BMI data better than did a single normal distribution. Genetic and environmental models that could explain both the familial aggregation and the mixture of normal distributions were investigated using complex segregation analysis. There was strong support for a single recessive locus with a major effect that accounted for almost 35% of the adjusted variation in BMI. Polygenic loci accounted for an additional 42% of the variation. Approximately 23% of the adjusted variation was not explained by genetic factors. For spouses living in the same household, their shared environment accounted for 12% of their variation. For siblings living in the same household, their shared environment accounted for 10% of their variation. While shared environments contributed to variation in adjusted BMI, more than 75% of the variation was explained by genetic factors that include a single recessive locus. Approximately 6% of the individuals in the population from which these pedigrees were sampled are predicted to have two copies of the recessive gene, while 37% of the individuals are predicted to have one copy of the gene.

Introduction

Obesity in adult life is associated with several chronic disorders including hypertension, atherosclerosis, diabetes mellitus, and certain cancers (Lew and Garfinkel 1979; Sims 1979; Barrett-Connor 1985; Bray 1985). Childhood obesity is predictive of obesity as an adult (Clarke et al. 1986), and the degree of obesity in adults has been shown to be an important long-term predictor of morbidity as well as mortality (Kannel 1983; Simopoulos and Van Itallie 1984; Van Itallie 1985). It has been estimated that approximately 35 million adult Americans are obese, defined, as body weight more than 20% above the ideal weight determined by NHANES II criteria (Van Itallie 1985).

Individual differences in ponderosity (body weight relative to height) are important predictors of differences in cardiovascular risk factor levels. A recent study of groups of students from Muscatine, IA, whose growth patterns over 4 years showed them to be either persistently the leanest, gaining ponderosity, or persistently the heaviest, relative to their peer group, reported that the students who had persistent excess weight for height had higher systolic blood pressure, higher triglyceride and apolipoprotein B levels, and lower high-density lipoprotein cholesterol (HDL-C) and apolipoprotein A-I levels, compared with the other students in the study (Burns et al. 1989*b*). The levels of ponderosity as measured by body mass index (BMI; kg/m^2) in the mothers, fathers, and siblings of these students clustered with

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the levels of BMI in the students. Overweight relatives in that study had higher blood pressure, total cholesterol, low-density lipoprotein cholesterol (LDL-C), and triglyceride levels and had lower HDL-C levels, compared with relatives who were not overweight (Burns et al. 1989*b*). When these risk factor levels were adjusted for the BMI differences among the relatives in the study, the differences between overweight and nonoverweight groups were no longer significant (Burns et al. 1989*b*). This suggested that being overweight has an adverse effect on coronary risk factor levels. Among the individuals, genetic differences at polygenic loci were found to explain 36%–52% of the variability in BMI across the range of ponderosity represented by these students and their relatives (Burns et al. 1989*b*).

BMI has a high correlation with body weight, body density, and skinfolds and has a low correlation with height (Montoye et al. 1965; Keys et al. 1972; Killeen et al. 1978; Roche et al. 1981; Cronk and Roche 1982). BMI is also linearly related to the desirable-weight index that is derived from the medium-frame Ideal Body Weight estimates (U.S. Department of Health, Education and Welfare 1979). The distribution of BMI has been reported to be positively skewed in several samples from the general population (Annest et al. 1983; Longini et al. 1984; Price et al. 1989). In one of these samples, the skewness in the distribution was explained by a mixture of normal distributions (Price et al. 1989). Several factors, both genetic and environmental, could explain such a mixture of distributions.

In determining BMI variability in the relatives of the schoolchildren from Muscatine, in the study reported herein we examined (*a*) the role of genetic factors, both at a single locus with a major effect on BMI and at polygenic loci, and (*b*) the role of shared environments between spouses and between siblings living in the same household. The present study presents evidence both for the segregation of a single locus with a major effect on the levels of BMI and for the effects of polygenic loci and shared environments.

Methods

On alternate years beginning in 1971, the heights, weights, triceps skinfold thicknesses, heart rates, blood pressures, and lipid levels of the children of Muscatine have been measured in the schools (Clarke et al. 1978). Muscatine, located on the Mississippi River in southeast Iowa, has a population of nearly 24,000 residents. The participation rate in each of these biennial surveys has been approximately 70% of the school-age population. The 1,783 students who participated in each of the school surveys conducted in 1977, 1979, and 1981 were eligible to serve as probands for The Muscatine Ponderosity Family Study.

Proband Identification

We proposed to study 70 families in each of the following four groups: (1) a *random group*—families of a random sample of all eligible students; (2) a *lean group*—families of students in the first quintile of relative weight on all three surveys; (3) a *heavy group*—families of students in the fifth quintile of relative weight on all three surveys; and (4) a *gain group*—families of students with a gain of at least two quintiles of relative weight from the first or second survey to the second or third survey. For each survey year, the relative weight (weight/median weight for the appropriate age, height, and gender group × 100) was determined for every participating student. The relative weights were rank ordered and grouped into quintiles. The quintile pattern from the three surveys was determined for each of the 1,783 potential probands. Nine hundred sixty-eight of these eligible students came from 326 families, each with more than one child, who had participated in each of the three surveys. Therefore, only the youngest eligible child in each family was retained as a potential proband, providing 1,141 potential probands for the study. Because 4 years had elapsed between the final survey used to define eligible students (in 1981) and the family study (in 1984–85), elimination of all except the youngest eligible child in each family provided the largest pool of unrelated probands still living in the local area. On the average, 25% of the lean, heavy, and gain probands selected because they were the youngest eligible child in a family had eligible siblings who were concordant with regard to potential study group.

To allow for refusals and ineligibility, 125 students were first randomly chosen from the 1,141, to serve as potential probands for the random group. This sample consisted of nine lean students, nine heavy students, 15 gain students, and 92 students with other quintile patterns. The unselected students who qualified to be probands in the lean (n = 92), heavy (n = 121), and gain (n = 118) groups were then eligible to be recruited for their respective study groups.

Each of the four lists of potential probands was randomized, and a recruiter, blinded as to which study group a particular list represented, began contacting

families, 25 at a time from each group, to explain the study protocol and to request their participation. If the recruiter determined that a student either was adopted, did not live with both natural parents, or had a growth-perturbing illness, that family was considered to be ineligible (31 of the 356 families contacted). Once a family agreed to participate (41 of those contacted refused), a trained genealogist obtained a complete pedigree including gender, age, and vital status information for all first-, second-, and third-degree relatives. Information about the pedigree was collected from each adult participant in a family. The 284 participating families were ascertained through 70 probands from the random group, 72 probands from the lean group, 70 probands from the gain group, and 72 probands from the heavy group. The 70 probands from the random group consisted of five lean students, five heavy students, six gain students, and 54 students with other quintile patterns. The 284 probands, as a group, showed an increase in both mean and variability (shown as mean ± SD) of BMI during the three school surveys, from 18.07 ± 3.87 in 1977, to 19.37 ± 4.47 in 1979, to 20.96 ± 4.70 in 1981. In 1981, BMI range was 12.82–34.65.

Pedigree Configuration

The members of each family targeted for examination during 1984–85 included the proband, parents, siblings, a related aunt or uncle, and a first cousin of the proband. The aunt or uncle and cousin invited to participate were chosen, first, on the basis of their geographic location. If multiple cousins were available, we attempted to examine a cousin who was of the same gender and closest in age to the proband. The family members, along with the proband, were asked to come, after an overnight fast, to a Muscatine clinic where the following were obtained: (1) blood samples; (2) blood pressures, pulse rates, and anthropometric measurements; and (3) medical histories. Three hundred forty-nine of the study participants could not come to the clinic but lived within 350 miles of Muscatine. A member of our field staff went to their homes to conduct the examination and to obtain a blood sample. Data for diabetic individuals and for those using thyroid medication or taking corticosteroids (n = 41) were eliminated from the present study, to make the sample identical to that in the previously published analyses of study data (Burns et al. 1989*b*). This yielded data on a total of 1,302 relatives and 278 probands.

Measurements

Heights and weights for probands and for their relatives were obtained (with subjects wearing indoor clothing and no shoes) by trained, certified observers. Height was recorded to the nearest 0.5 cm by using an Iowa anthropometric plane and square. Weight was recorded to the nearest 0.1 kg by using a portable digital readout scale (Heathkit GD-1186) that was calibrated daily.

Statistical Analysis

Using polynomial regression analysis, we estimated, for males and females separately within each relative type (probands, siblings, parents, aunts/uncles, and cousins), the extent to which variation in BMI was attributable to differences in age and age^2. All subsequent analyses were performed on the adjusted BMI levels obtained by adding the overall sample mean to the residuals from the polynomial regression within each of the 10 gender × relative types. Interclass and intraclass correlations were estimated, to assess familial aggregation (Bailey-Wilson and Elston 1989) among the various relatives, with the probands being excluded.

Maximum likelihood methods (Day 1969) were used to determine whether the distribution of adjusted BMI levels in the relatives could be explained by a mixture of normal distributions. This analysis also excluded the probands. A model with a mixture of three normal distributions with equal variances was compared with a model with a mixture of two normal distributions with equal variances. The six parameters of the three-component model include the means of each component, the relative frequency of the first two components, and the within-component SD. The difference between the maximum of the $\log_e$ likelihoods under the two models being compared forms a basis for judging whether a mixture of two distributions fits the data as well as does a mixture of three distributions. Twice the difference between the two $\log_e$ likelihoods is distributed approximately as a χ^2 distribution with df equal to the number of parameters restricted by the hypothesis, i.e., two. When a model with a mixture of two distributions could not be rejected, then a model with a mixture of two distributions was compared with a model with one normal distribution.

Several factors, both genetic and environmental, could lead to the rejection of a single normal distribution, in favor of a mixture of distributions fitting the

data. Complex segregation analysis (Elston and Stewart 1971; Lalouel et al. 1983) was used to test a specific series of models that represent combinations of these factors. We assumed that the observed distribution of the quantitative trait, adjusted BMI, is a consequence of the independent contributions of the following: a single genetic or nontransmitted environmental factor with a major effect on BMI levels, the additive allelic effects of a large number of independent polygenic loci each with a small effect, the effects of shared environments, and individual-specific environmental influences. The major factor was modeled as having two alternatives, L (leaner) and H (heavier), that may be of either genetic or nontransmitted environmental origin. These combine to define three classes, or ousiotypes (Cannings et al. 1978), of individuals, denoted LL, LH, and HH. The relative frequency of L is denoted p and the relative frequency of H is denoted q (equals $1 - p$). If Hardy-Weinberg equilibrium in the population being sampled is assumed, then the relative frequency of LL, LH, and HH individuals is p^2, $2pq$, and q^2, respectively.

Other parameters of this model include the phenotypic mean of each ousiotype (μ_{LL}, μ_{LH}, and μ_{HH}) and the phenotypic variance (σ^2) among individuals with the same ousiotype. It is assumed that $\sigma^2 = \sigma^2_{LL} = \sigma^2_{LH} = \sigma^2_{HH}$. The model partitions this variance into a fraction that is attributable to the additive effects of the polygenic loci (h^2), a fraction that is attributable to shared environmental effects, and a fraction that is attributable to individual-specific environmental effects and measurement error. The following two types of shared environments were included in the model: (1) an effect shared by spouses living in the same household at the time of the family study (Spouse E) and (2) an effect shared by siblings living in the same household at the time of the family study (Sib E). For each defined shared effect in the model, all members of a pedigree who shared this effect were denoted with the same arbitrarily selected unique positive number, while anyone who did not share this effect with anyone else was assigned a value of zero (Hasstedt 1989, 1991). For a single shared effect, the number only has to be unique within a pedigree. This is equivalent to the method of denoting shared environments that has been used elsewhere (Lange et al. 1976; Moll et al. 1979; Hasstedt et al. 1985).

τ_1, τ_2, and τ_3 are the probabilities that individuals of ousiotypes LL, LH, and HH, respectively, transmit the L factor to their offspring. For the general transmission model (Lalouel et al. 1983), these transmission probabilities were each estimated under the constraint that they be 0–1. The single-locus Mendelian model defines the probabilities of transmitting alleles from parents to their offspring as being $\tau_1 = 1.0$, $\tau_2 = .5$, and $\tau_3 = 0$. The nontransmitted environmental factor model, on the other hand, predicts that the probability that an individual is either one ousiotype or another is independent of both (*a*) his or her generation and (*b*) the ousiotypes of his or her parents (Elston and Stewart 1971). Under this model, each of the transmission probabilities is taken to be equal to the relative frequency of L, which is p.

Testing hypotheses about parameters corresponds to restricting one or more parameters to specific hypothesized values, while estimating the remaining parameters from the data. Twice the difference between the maximum of the $\log_e$ likelihood of a model with unrestricted parameters and the maximum of the $\log_e$ likelihood of a model with restricted parameters is distributed approximately as a χ^2 when the null hypothesis is true. The df for this χ^2 test are equal to the number of parameters restricted to values stated by the hypothesis. Among the models considered, the model with unrestricted parameters is the general transmission model in which τ_1, τ_2, and τ_3 as well as p, μ_{LL}, μ_{LH}, μ_{HH}, σ^2, h^2, Spouse E, and Sib E, are estimated. If another model with restricted parameters could not be rejected when compared with this general transmission model, we then compared the reduced model with the restricted parameters with other models with further parameter restrictions, so that all of the model comparisons were nested.

First we tested hypotheses to establish the optimal transmission parameterization of the major factor (among those considered), while not restricting any of the ousiotype means to be equal and while including the effects of polygenic loci as well as of the shared environments. Then, using the transmission parameterization obtained in the earlier hypothesis testing, we tested hypotheses to establish whether constraining two of the ousiotype means to be equal could explain the data ($\mu_{LL} = \mu_{LH} < \mu_{HH}$, and $\mu_{LL} < \mu_{LH} = \mu_{HH}$) as well as could a model not restricting any ousiotype means to be equal ($\mu_{LL} < \mu_{LH} < \mu_{HH}$). Finally, we tested hypotheses that the contributions from the polygenic loci and/or the shared environmental effects were not different from zero.

The likelihoods of the models were computed using the Pedigree Analysis Package (PAP) (Hasstedt et al. 1979; Hasstedt 1989), which employs an approximation to the exact likelihood of a model that includes

both a single factor as well as polygenic loci and shared environmental factors (Hasstedt 1991). The likelihood for each model considered was maximized using a quasi-Newton method (Lalouel 1979). Since ascertainment was necessarily single, we corrected for ascertainment by conditioning on the adjusted BMI level of the proband in each pedigree (Cannings and Thompson 1977; Hopper and Mathews 1982; Boehnke and Lange 1984; Young et al. 1988). Parameter estimates associated with a given model were taken to be those that maximized the corresponding likelihood.

Results

Table 1 describes the distribution of age, height, and weight in the probands and in their relatives from the family survey. Table 2 presents the unadjusted BMI according to relative type and gender, the proportion of BMI variation due to differences in age and age^2 for the different relatives in the study, and the correlation between adjusted BMI and height and weight. The proportion of BMI variation due to age differences ranged from 0.34% in the fathers of the probands to 36.03% in the male cousins of the probands. Only for the fathers was the adjusted BMI–height correlation coefficient significant. The adjusted BMI–weight correlation coefficients were all significantly different from zero ($P < .01$).

There was significant familial aggregation of adjusted BMI in these pedigrees (table 3). The interclass correlation was .17 ($P < .05$) between spouses and .22 ($P < .0001$) between parents and their offspring (excluding the probands). The estimate of the intraclass correlation for the siblings of the probands was .35 ($P < .0001$).

The distribution of adjusted BMI for the 1,302 relatives is shown by the histogram in figure 1. From commingling analysis, the hypothesis that a mixture of two component distributions fits the adjusted data as well as does a mixture of three component distributions was not rejected ($\chi^2 = 0.002$, df = 2; data not shown), while the hypothesis that a single normal distribution fits the adjusted data as well as does a mixture of two distributions was rejected ($\chi^2 = 212.73$, df = 2, $P < .0001$; data not shown). On the basis of the maximum likelihood parameter estimates, the sample predicts (1) that 7.5% of the population from which these individuals were drawn falls in the upper component distribution, with its BMI mean at 34.59, and (2) that 92.5% falls in the lower component, with its BMI mean at 23.36. Each component has an SD of 3.395. The component distributions are displayed in figure 1.

For adjusted BMI, the total sample skewness was 1.623, and the skewness in the relatives of the probands was 1.758. The hypothesis that the adjusted BMI levels were normally distributed was rejected using the Lilliefors test ($P < .05$), both for the total sam-

Table 1

Age, Height, and Weight, by Relative Type and Gender

Subject (N)	Age (years)		Height (cm)		Weight (kg)	
	Range	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)
Proband:						
Male (128)	12.6–24.2	16.3 (2.4)	143.3–189.8	172.9 (9.7)	36.7–137.7	69.2 (17.6)
Female (150)	12.4–22.2	16.7 (2.5)	141.3–180.6	164.0 (6.3)	37.4–104.9	60.7 (13.6)
Sibling:						
Male (221)	4.7–36.6	19.9 (6.6)	102.1–196.2	171.2 (16.3)	17.3–122.8	69.5 (20.8)
Female (213)	4.9–38.2	20.6 (6.9)	95.6–179.4	160.6 (12.3)	16.1–117.1	58.7 (15.6)
Father (232)	32.4–66.1	46.0 (6.9)	157.1–196.7	177.3 (6.4)	55.0–147.9	85.3 (12.6)
Mother (251)	30.5–64.7	43.3 (6.6)	142.0–181.3	163.8 (5.6)	41.2–136.4	70.0 (14.9)
Uncle (82)	25.8–67.2	44.3 (8.1)	164.7–191.5	178.0 (5.7)	51.8–144.0	84.5 (13.1)
Aunt (115)	14.2–65.4	42.6 (8.9)	140.4–178.5	161.6 (5.8)	43.3–124.2	68.0 (13.7)
Cousin:						
Male (97)	5.0–34.2	16.2 (5.7)	109.2–190.4	165.1 (17.9)	19.0–97.3	59.1 (18.3)
Female (91)	4.9–39.1	16.1 (6.7)	111.7–178.1	155.0 (16.0)	18.2–148.2	52.9 (18.4)
Pooled (1,580)	4.7–67.2	29.4 (14.5)	95.6–196.7	167.3 (12.8)	16.1–148.2	68.6 (18.7)

Table 2

BMI, by Relative Type and Gender

Subject (*N*)	BMI					
				Relationship to Age, Height, and Weight[a]		
				Proportion of Variation in BMI Explained by Age and Age^2 ($R^2 \times 100$)	Correlation between Adjusted BMI and	
	Minimum	Maximum	Mean (SD)		Height	Weight
Proband:						
Male (128)	14.56	40.98	23.01 (5.20)	3.27 (NS)	−.020 (NS)	.844****
Female (150)	15.63	38.30	22.53 (4.84)	9.23**	−.089 (NS)	.887****
Sibling:						
Male (221)	14.98	39.96	23.14 (4.73)	32.60****	.004 (NS)	.558****
Female (213)	13.82	38.28	22.42 (4.55)	18.10***	−.015 (NS)	.687****
Father (232)	18.49	55.12	27.16 (3.97)	.34 (NS)	−.190**	.858****
Mother (251)	16.19	52.75	26.11 (5.52)	.87 (NS)	−.116 (NS)	.942****
Uncle (82)	17.28	40.95	26.66 (4.03)	.61 (NS)	−.183 (NS)	.898**
Aunt (115)	18.20	48.39	26.02 (5.15)	5.92*	−.053 (NS)	.924**
Cousin:						
Male (97)	13.89	33.13	21.03 (3.82)	36.03***	.005 (NS)	.457**
Female (91)	12.98	63.72	21.52 (6.03)	22.42***	−.149 (NS)	.599**
Pooled (1,580)	12.98	63.72	24.21 (5.25)	. . .	−.047 (NS)	.639**

[a] NS = not significant.
* $P < .05$.
** $P < .01$.
*** $P < .001$.
**** $P < .0001$.

ple and for a sample with the probands excluded (Conover 1971). For a trait whose distribution is skewed, consideration of a model with both a single genetic factor that has a major effect on the trait and polygenic loci as the most general model may lead to the false inference that a single locus exists (MacLean et al. 1975). However, normalizing transformations of a biologically skewed trait can lead to a large reduction in the power to detect the presence of a single locus with a major effect when such a locus exists (MacLean et al. 1976). As an alternative explanation for the mixture of distributions, the inclusion of a model with a nontransmitted environmental factor that may have a major effect on the trait reduces the possibility that skewness alone will lead to a false inference regarding the presence of a single locus with a major effect (Demenais et al. 1986). Because of these considerations, no normalizing transformation was applied to these data.

Table 3

Correlations between 1,302 Relatives,[a] for Adjusted BMI

Relatives (N^b)	Correlation[c]
Spouses[d] (215)	.17*
Parent-offspring[d] (920)	.22****
Siblings[e] (332)	.35****
Uncle/aunt-nephew/niece[d] (490)	.09*
Cousins[e] (316)	.08 (NS)

[a] Excluding probands.
[b] Number of pairs.
[c] NS = not significant.
[d] Interclass correlation where members of pairs can be distinguished by reason of gender or generation.
[e] Intraclass correlation where members of pairs can not be distinguished.
* $P < .05$.
**** $P < .0001$.

Table 4 presents the maximum likelihood estimates of the parameters under five different models and also presents the associated χ^2 statistics for testing hypotheses about restricted parameters in the different models. In the unrestricted (general transmission) model (model 1 in table 4) all 11 of the parameters were estimated. The four reduced models (models 2–5 in table 4) also included a major factor, polygenic

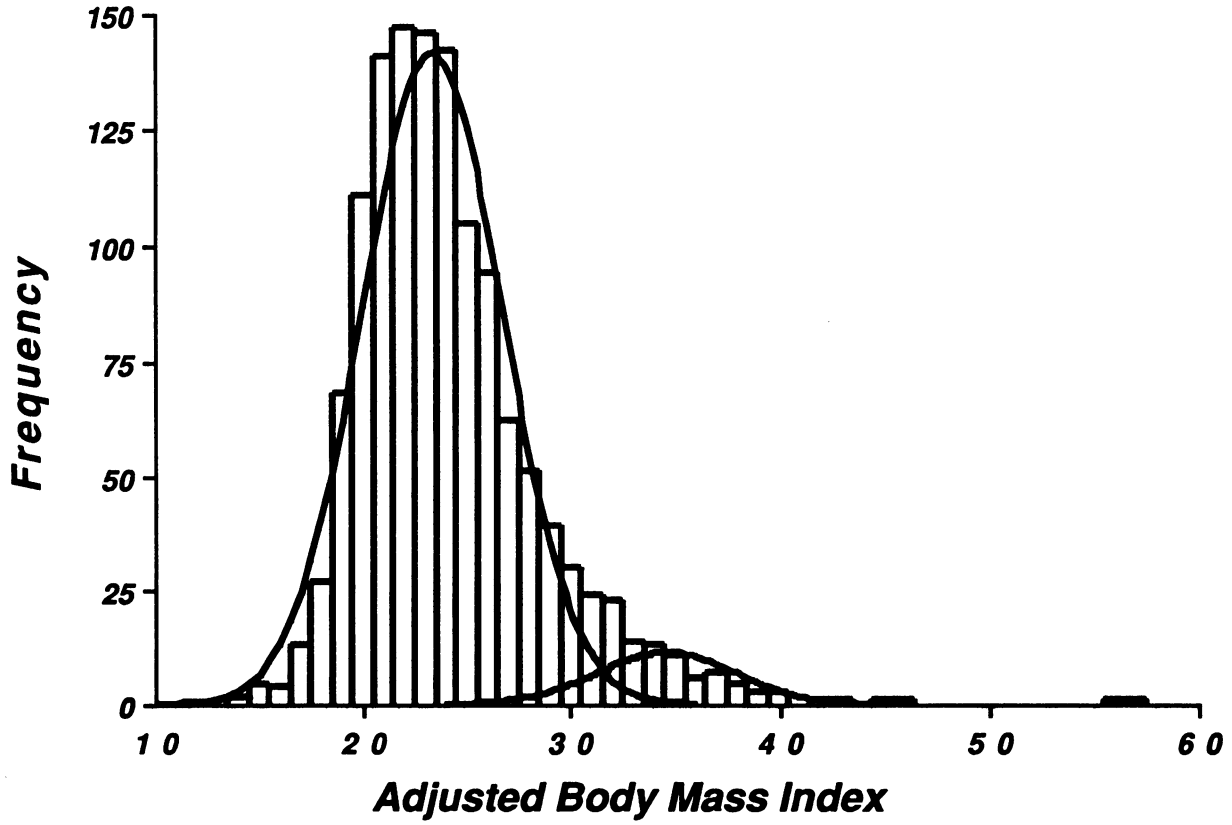

Figure 1 Distribution of adjusted BMI for 1,302 relatives studied with two-component distributions predicted from parameter estimates from commingling analysis.

loci, and shared environmental effects. The model which included both a nontransmitted environmental factor responsible for the mixture of distributions ($\tau_1 = \tau_2 = \tau_3 = p$) plus the effects of polygenic loci and shared environmental effects (see model 2 in table 4; $\chi^2 = 31.42$, $P < .0001$) was rejected. The model that included a single locus ($\tau_1 = 1.0$, $\tau_2 = .5$, and $\tau_3 = 0$) plus polygenic loci and shared environmental effects (model 3 in table 4; $\chi^2 = 4.42$, $P > .20$) could not be rejected when compared with the Model 1, the general transmission model. Models 4 and 5 in table 4 included a single locus ($\tau_1 = 1.0$, $\tau_2 = .5$, and $\tau_3 = 0$), with two of the single-locus genotype means constrained to be equal to one another. Model 4, which assumed that H was dominant to L, was rejected when compared with model 3 ($\chi^2 = 69.40$, $P < .0001$). However, model 5, which assumed that H was recessive to L, was not rejected when compared with model 3 ($\chi^2 = 2.60$, $P > .10$). Among the models considered here, a model with a recessive single locus, polygenic loci, and shared environmental effects gave the best fit to the data. The maximum likelihood parameter estimates under model 5 predict that, in the population from which these pedigrees were selected, a single recessive major locus and polygenic loci explain, respectively, 34.59% and 42.19% of the total adjusted BMI variation. There is 23.33% of the adjusted variation that is not explained by genetic factors. For spouses living in the same house, their shared environment explains 12.10% of their adjusted variation. For siblings living in the same house, their shared environment explains 10.27% of their total adjusted BMI variation. This model also predicts that 6.05% of the individuals in the population from which these pedigrees were sampled have the HH genotype and that 37.10% of the individuals are predicted to have one copy of the H gene.

When the model with a single recessive major locus,

Table 4

Maximum-Likelihood Parameter Estimates ± Standard Errors (SEs) and χ^2 Statistics for Testing Hypotheses to Establish Transmission Parameterization

Parameter	Maximum-Likelihood Estimate ± SE for Model[a]				
	1 General Transmission	2 Nontransmitted Factor	3 Single Locus	4 Dominant Single Locus	5 Recessive Single Locus
p	.737 ± .03	.770 ± .02	.754 ± .02	.979 ± .01	.754 ± .02
μ_{LL}	23.37 ± .32	23.97 ± .27	23.37 ± .30	24.01 ± .18	23.76 ± .17
μ_{LH}	24.26 ± .40	23.98 ± .40	24.25 ± .37	37.21 ± 1.2	23.76 ± .17
μ_{HH}	34.57 ± .64	34.93 ± .71	35.04 ± .67	37.21 ± 1.2	34.80 ± .63
σ	3.55 ± .11	3.68 ± .11	3.57 ± .11	3.92 ± .11	3.62 ± .10
h^2	.644 ± .10	.654 ± .09	.615 ± .07	.513 ± .06	.645 ± .09
Spouse E	.217 ± .10	.235 ± .09	.189 ± .10	.227 ± .08	.185 ± .10
Sib E	.162 ± .06	.171 ± .05	.161 ± .06	.176 ± .05	.157 ± .06
τ_1	[1.0]	.770 ± .02	(1.0)	(1.0)	(1.0)
τ_2	.441 ± .05	.770 ± .02	(.5)	(.5)	(.5)
τ_3	.514 ± .18	.770 ± .02	(0)	(0)	(0)
$\log_e$ L	−6,581.00	−6,596.71	−6,583.21	−6,617.91	−6,584.51
χ^2:					
Comparison with model 1		31.42****	4.42 (NS)		
df		3	3		
Comparison with model 3				69.40****	2.60 (NS)
df				1	1

[a] Parentheses denote that value is fixed in model; brackets denote that value is at boundary. NS = not significant.
**** $P < .0001$.

polygenic loci, and shared environmental factors (model 5 in tables 4 and 5) was compared with models having further restrictions (models 6–12 in table 5), the χ^2 statistics were 3.88–377.08. Each model that did not include the effects of a single recessive locus (see models 7 and 12) or that did not include the effects of polygenic loci (see models 6, 9, and 12) was rejected. Models that did not include the effects of any shared environmental factors (see models 6, 8, and 12) were also rejected. The model that included the single recessive locus, polygenic loci, and the spouse shared environmental effect (see model 10) was rejected when compared with model 5 ($\chi^2 = 7.04$, df = 1, $P < .01$); the model that included the single recessive locus, polygenic loci, and the sibling shared environmental effect (see model 11) was also rejected when compared with model 5 ($\chi^2 = 3.88$, df = 1, $P < .05$). On the basis of these model comparisons, these data suggest that in the population from which these pedigrees were sampled there is evidence that the distribution of adjusted BMI is influenced to a small extent both by environmental factors shared by siblings living in the same house and by environmental factors shared by spouses living together. However, there is evidence that more than 75% of the variation in adjusted BMI is influenced by genetic factors that include both a single recessive major locus and polygenic loci.

Discussion

The observation of strong familial correlations for BMI (Mueller 1983; Heller et al. 1984; Longini et al. 1984) does not ensure that genes are involved in the determination of BMI, since individuals in families share environments as well as genes. Earlier genetic analyses of family BMI data that only considered polygenic loci reported that both genes and shared environmental factors explain the observed correlations among relatives (Longini et al. 1984; Bouchard et al. 1985; Stunkard et al. 1986*a*; Hunt et al. 1989; Sorensen et al. 1989). The observed correlations between relatives in our study are consistent with the parameter estimates we obtained for the most parsimonious model (model 5 in table 5). Since, on the basis of their single-locus genotype (either the LL or LH genotype), 94% of the sample is expected to have the same pheno-

Table 5

Maximum-Likelihood Parameter Estimates ± Standard Eerrors (SEs) and χ^2 Statistics for Testing Hypotheses Regarding Polygenic and Shared Environmental Effects (E) between Spouses and Siblings

	Maximum-Likelihood Estimate ± SE for Model[a]							
Parameter	5 Recessive Single Locus + Polygenes + E	6 Recessive Single Locus	7 Polygenes + E	8 Recessive Single Locus + Polygenes	9 Recessive Single Locus + E	10 Recessive Single Locus + Polygenes + Spouse E	11 Recessive Single Locus + Polygenes + Sib E	12 No Single Locus, No Polygenes, No E
p	.754 ± .02	.706 ± .02	(1.0)	.755 ± .02	.726 ± .02	.755 ± .02	.753 ± .02	(1.0)
μ_{LL}	23.76 ± .17	23.28 ± .17	24.41 ± 1.9	23.71 ± .16	23.44 ± .13	23.73 ± .17	23.74 ± .16	24.23 ± .12
μ_{LH}	23.76 ± .17	23.28 ± .17	24.41 ± 1.9	23.71 ± .16	23.44 ± .13	23.73 ± .17	23.74 ± .16	24.23 ± .12
μ_{HH}	34.80 ± .63	33.64 ± .61	24.41 ± 1.9	34.89 ± .62	34.07 ± .64	34.85 ± .64	34.83 ± .61	24.23 ± .12
σ	3.62 ± .10	3.37 ± .10	4.56 ± .11	3.56 ± .09	3.48 ± .09	3.59 ± .10	3.59 ± .10	4.50 ± .09
h^2	.645 ± .09	(0)	.582 ± .06	.598 ± .05	(0)	.659 ± .06	.594 ± .06	(0)
Spouse E	.185 ± .10	(0)	.211 ± .07	(0)	.160 ± .11	.202 ± .09	(0)	(0)
Sib E	.157 ± .06	(0)	.216 ± .05	(0)	.443 ± .06	(0)	.172 ± .06	(0)
$\log_e$ L	−6,584.51	−6,649.30	−6,688.53	−6,590.56	−6,632.53	−6,588.03	−6,586.45	−6,773.05
χ^2: comparison with model 5		129.58****	208.04****	12.10**	96.04****	7.04**	3.88*	377.08****
df		3	2	2	1	1	1	5

[a] In all models considered, $\tau_1 = 1.0$, $\tau_2 = .5$, $\tau_3 = 0$. Parentheses denote that value is fixed in model.

* $P < .05$.

** $P < .01$.

**** $P < .0001$.

typic mean, we can obtain estimates of expected correlations from the parameters in model 5 in table 5. Under the assumption of similar phenotypic means, the expected correlation between siblings would be (*a*) one-half the estimate of the contribution from polygenic loci, among individuals with the same single-locus genotypic mean (.645 divided by 2 from h^2 in model 5 in table 5), and (*b*) all of the estimated Sib E (.157 in model 5 in table 5). The observed correlation between siblings was .35, and the expected value was .48. For spouses with the same mean phenotype because of the single-locus genotype, the expected correlation is .185 (from Spouse E in model 5 in table 5), and the observed value was .17. For parents and offspring with the same mean phenotype because of their single-locus genotype, the expected correlation was .32 (.645 divided by 2 from h^2 in model 5 in table 5), and the observed value was .22. The observed correlations were lower than the expected values because the estimates of the expected correlations do not take into account that some pairs of relatives will have different phenotype means because one of them will carry two copies of the H gene and thus be in the upper-component distribution while the other is LL or LH and in the lower-component distribution.

Our findings of significant familial correlations are also consistent with results of adoption studies. Early adoption studies showed both a significant association between parents and their natural children and a nonsignificant association between parents and their adoptive children (Biron et al. 1977; Hartz et al. 1977; Bouchard et al. 1982), and an adoption study (Stunkard et al. 1986*b*) which obtained body size information on both biologic and adoptive parents showed a significant association between adoptees and their biologic parents but not between adoptees and their adoptive parents. These results are all consistent with the involvement of genetic factors in the familial aggregation of BMI.

Other studies have confirmed that genes play a strong role in the familial clustering of the levels of BMI (Longini et al. 1984; Bouchard et al. 1985; Stunkard et al. 1986*a*; Hunt et al. 1989; Sorensen et al. 1989). These studies did not consider the role of

a single locus with a major effect. Some of these family studies have also reported a small (less than 7%) but significant contribution from the Sib E effect (Longini et al. 1984).

In our study of the BMI of 1,580 individuals from 284 families from Muscatine, we found evidence both for a single recessive locus that explains 34.59% of the variability in BMI and for polygenic loci which explain an additional 42.19% of the variability. We estimate that 37.10% of the individuals in this population are carriers of the recessive gene and that 6.05% are homozygous for the gene.

Three other studies have recently suggested that there is a substantial genetic component in the determination of BMI and that some of the genes involved are not acting additively (Price et al. 1990; Province et al. 1990; Stunkard et al. 1990). From an analysis of the BMI of MZ twins reared together and apart and of DZ twins reared together and apart, Stunkard et al. (1990) concluded that sharing the same environment early in life did not contribute to the similarity of BMI later in life. They estimated the heritability of BMI to be 74% for men and 69% for women, with 17% and 32%, respectively, being attributable to additive genetic variance and the remainder being nonadditive. Price et al.'s (1990) segregation analysis of BMI in 961 randomly ascertained families in the Lipid Research Clinics family studies suggested a recessive mode of inheritance for a single gene with large effects as well as polygenic loci. Province et al.'s (1990) segregation analysis of 3,281 nuclear families from Tecumseh, MI, also found evidence for a single recessive locus with large effects as well as polygenic loci.

The results from our study and the studies of Price et al. (1990), Province et al. (1990), and Stunkard et al. (1990), which suggest a substantial nonadditive component in the determination of BMI, in contrast to previous studies which showed only a substantial additive polygenic component, are due not only to the more complex models that have been fitted to the data but also to the sampling designs that have been used to identify individuals for examination. Our study design called for one-quarter of the families to be ascertained through a child who showed a persistent pattern of excess ponderosity. This overrepresentation in the upper tail of the BMI distribution resulted in more statistical power to identify major-gene effects. The design for the twin study (Stunkard et al. 1990) included twins reared apart, and this allowed a more complete investigation of the genetic and environmental components of BMI. The large number of randomly ascertained families in the studies by Price et al. (1990) and Province et al. (1990) also provided sufficient statistical power to identify major-gene effects if they were present.

A major unanswered question is, What inherited factors carry an associated risk for excess ponderosity? There are probably multiple mechanisms, and the specific mechanisms and specific genes may vary among families. A number of possible factors exist, including genes associated with basal metabolism, dietary thermogenesis, appetite, satiety, endocrine function, and fat storage. Variation in basal metabolic rate (BMR) among individuals has been shown to be due in part to genetic differences (Bogardus et al. 1986; Bouchard et al. 1989). In obese adolescents, BMR and total energy expenditure are not reduced compared with those in nonobese adolescents (Bandini et al. 1990). Therefore these factors do not appear to be involved in the maintenance of obesity in children, but they may be involved in the initiation of obesity. The response to overfeeding has been shown to have a substantial genetic component as assessed by overall body weight, percentage of fat, fat mass, and estimated subcutaneous fat (Bouchard et al. 1990).

The genes for several peptides that are known to inhibit food intake and to be related to satiety have been cloned and sequenced (Goodman et al. 1980; Deschenes et al. 1984; White and Saunders 1986), and these may provide clues in some individuals. In Mexican-Americans an association has been found between an RFLP of the human insulin receptor gene and obesity (Raboudi and Frazier 1989). Several other candidate genes have been suggested, such as lipoprotein lipase and sex hormone–binding globulin as reviewed by Schull and Hanis (1990).

In humans, there are a number of very rare syndromes (e.g., Prader-Willi syndrome and Bardet-Biedl syndrome) that include the obesity phenotype and that follow a recessive pattern of inheritance. Many domestic animals are bred for a particular amount and distribution of body fatness, and, while the breeding process is very successful in producing the desired type of animals, in most species the genes that are being selected have not been specifically identified. There are, however, several rodent models of obesity that have been extensively characterized. In the Zucker fatty (fa/fa) rat (Zucker and Zucker 1961), the diabetic (db/db) mouse, and the obese (ob/ob) mouse, obesity is inherited as an autosomal recessive trait. In each of these models, metabolic abnormalities have been identified that may be responsible for the obesity.

The gene responsible for the db trait has been mapped to the murine chromosome 4, and that for the ob trait has been mapped to the murine chromosome 6 (Friedman et al. 1988). The Zucker fatty rat has both an altered energy metabolism and altered responses to insulin and glucocorticoids (Bazin and Lavau 1982; Lavau et al. 1985; Zaninetti et al. 1989). The db/db mouse and the ob/ob mouse also exhibit altered responses to insulin and glucocorticoids (Coleman 1982; Tokuyama and Himms-Hagen 1987).

In humans, excess ponderosity is associated with increased coronary risk. The adverse effect of increased BMI on coronary morbidity and mortality has been attributed to both its positive association with blood pressure and LDL-C and its negative association with HDL-C (Hubert 1986; Hubert et al. 1987). In Framingham participants younger than age 50 years, obesity conveyed an increased risk of coronary heart disease even when it was unaccompanied by borderline or definite hypertension, hypercholesterolemia, cigarette smoking, glucose intolerance, or left-ventricular hypertrophy (Hubert et al. 1983). Obesity has been shown to cause insulin resistance, which has renal effects (e.g., sodium retention), central nervous system effects (e.g., increased sympathetic tone), and liver effects (e.g., increased very-low-density-lipoprotein production and lower high-density-lipoprotein production) (Landsberg 1986; Reaven 1988).

In the sample described here, both the children and adults who were probably homozygous for the HH genotype have higher blood pressure, higher triglyceride levels, and lower HDL-C levels than do those who are probably heterozygous (LH) or homozygous for the LL genotype (Burns et al. 1989*a*). This suggests that those whose obesity is caused by a gene at a single locus with a major effect are at higher coronary risk, because of mechanisms associated with their coronary risk factor profile. When a gene at a single locus with a major effect that contributes to variation in BMI in humans is identified, it will have the potential to predict (1) individuals with a genetic predisposition to developing obesity and (2) those at risk for hypertension and atherosclerosis.

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