Am. J. Hum. Genet. 52:967-973, 1993

Segregation Analysis of Fat Mass and Other Body Composition Measures Derived from Underwater Weighing

Treva Rice,* Ingrid B. Borecki,* Claude Bouchard,‡ and D. C. Rao*,†

*Division of Biostatistics and †Departments of Psychiatry and Genetics, Washington University School of Medicine, St. Louis; and ‡Physical Activity Sciences Laboratory, PEPS, Laval University, Ste-Foy, Québec

Summary

Segregation patterns of three body composition measures which were derived from underwater weighing were evaluated in a random sample of 176 French-Canadian families. Two of the variables can be considered as primary partitions of weight (fat mass [FM] and fat-free mass [FFM]), while the remaining variable (percent body fat [%BF]) is a derived index combining the measures of both fat and fat-free weight. This study represents the first report investigating major gene effects for these measures. Segregation analyses revealed that a major locus hypothesis could not be rejected for two of the three phenotypes. The single exception was FFM, for which nearly 60% of the variance was accounted for by a non-Mendelian major effect, which may reflect environmentally based commingling or may be in part a function of gene-environment interactions or correlations. In contrast to the results for FFM, the results for each of FM and %BF were similar and suggested a major locus which accounted for 45% of the variance, with an additional 22%–26% due to a multifactorial component. Given the similarity of the major gene characteristics for these two phenotypes, the possibility that the same gene underlies both measures warrants investigation. A reasonable hypothesis is to consider genes that may influence nutrient partitioning, as the family of candidate genes to receive the major attention.

Introduction

The etiology of human obesity represents an important research area because of its association with the increased risk of noninsulin-dependent diabetes mellitus, hypertension, and cardiovascular disease (Burton et al. 1985; Kral 1985). However, there are few family studies assessing body fat (for review, see Bouchard and Pérusse 1988), by using measures such as percent of body fat (%BF; as assessed by underwater weighing techniques), as well as fat mass (FM) and fat-free mass (FFM; both computed from %BF and body mass). Path analyses of these three measures yield polygenic heritabilities of 22%, 15%, and 29%, respectively (Bouchard et al. 1988). Sibling and twin analyses (Bouchard et al. 1985) lead to much higher estimates for FM (40% and 99% for sibs and twins, respectively) and FFM (52% and 80% for sibs and twins, respectively). No studies investigating major gene hypotheses for these measures have been conducted to date.

The current study represents the first major gene investigation of body composition variables, based on underwater weighing. Two of these measures (i.e., FM and FFM) may be considered primary partitions of weight, as compared with the other variable, %BF, which combines measures of fat mass and lean mass. Previous commingling analyses of these three variables (Borecki et al. 1991) suggested a mixture of distributions only for the combination variable (i.e., %BF), consistent with a major gene hypothesis.

Subjects and Methods

Sample

The Québec Family Study consists of 1,630 individuals living within 80 km of Québec City, who were recruited through the media during the years 1978–81 to study the genetic effects on several physiological and biochemical traits. The parents (N = 727) ranged in age

Received March 5, 1992; final revision received December 23, 1992.

Address for correspondence and reprints: Treva Rice, Ph.D., Division of Biostatistics, Washington University School of Medicine, Box 8067, 660 South Euclid, St. Louis, MO 63110.

0002-9297/93/5205-0014$02.00

Table 1

Number of Individuals and Families

Variable	No. of Individuals	No. of Families
FM	616[a]	175[a]
FFM	619	176
%BF	619	176

[a] The slightly smaller sample size for FM reflects three sparse outlying offspring who were deleted from the analysis sample (age/sex corrected Z score > 5.1).

from 30.2 to 59.5 years, and offspring (N = 903) ranged in age from 8.4 to 25.7 years. The total sample of 375 nuclear families (parents and offspring) contains twin and adopted offspring, as well as a few cousins and stepparents. For the purposes of data adjustments (i.e., age and sex corrections) all individuals were retained. However, for the segregation analyses reported here, the family structure was modified such that only traditional nuclear families remained (i.e., parents and biological offspring), by deleting (*a*) one MZ cotwin from each twin pair, (*b*) all adopted offspring, and (*c*) all cousins and stepparents. A total of 325 individuals were excluded from the segregation analyses by these procedures (for details concerning data exclusions, see Pérusse et al. 1989). In addition, sparse outliers, defined as those individuals whose age/sex-adjusted scores (discussed later) were >4.0 SDs from the mean *and* were separated by at least 1 SD from the nearest internal score, were also deleted from the analyses. Only three individuals were defined as sparse outliers for one variable (FM). Finally, these measures were assessed in approximately half of the sample, since the equipment for underwater weighing was available only for the last half of the data collection phase. After accounting for family structure, sparse outliers, and missing data, the final sample sizes are given in table 1.

Measures

The three phenotypes analyzed in the present study are summarized in table 1. FM and FFM are computed from the measurement of body mass and %BF, with the latter assessed by an underwater weighing technique (Himes and Bouchard 1985). For a more complete description of the measures, reliabilities, and validities, see Bouchard et al. (1985).

Data Adjustments

All variables were adjusted for the effects of age, separately within four groups (fathers, mothers, sons, and daughters), in both the mean and the variance, by using multiple regression. Complete details are found in Borecki et al. (1991). In summary, each obesity measure was regressed on up to a third-degree polynomial in age in a stepwise manner, retaining terms significant at the 5% level. The residual variance resulting from the mean regression was also examined for age effects (i.e., heteroscedasticity) by regressing the squared residual on another cubic polynomial in age in a stepwise manner and by retaining significant terms (5%). Age accounted for 1%–11% of the variance in FM and 1%–15% in %BF. For FFM, age effects accounted for 3%–8% of the variance in parents and 65%–73% of the variance in offspring. Minimal age effects in the variance were found (i.e., little heteroscedasticity).

Segregation Analysis

Segregation analysis was carried out using the unified mixed model (Lalouel et al. 1983) as implemented in the computer program POINTER (Lalouel and Morton 1981; Morton et al. 1983). Analyses were performed by calculating the likelihood of offspring phenotypes, conditional on parental phenotype values. The mixed model assumes that a phenotype is composed of the independent and additive contributions from a major transmissible effect, a multifactorial background, and a normally distributed residual. The major effect is assumed to result from the segregation at a single locus having two alleles (i.e., **A** and **a**). There are seven parameters in the model: the overall variance (V); the overall mean (u); the major locus gene frequency (q); the displacement between the two homozygous means (t); the relative position of the heterozygous mean, or dominance (d); and two parameters representing the multifactorial heritabilities in children (H) and parents (HZ).

The unified mixed model also incorporates transmission probabilities of the major effect. The three transmission probabilities are τ_1 (the probability that an **AA** individual transmits allele **A** to the offspring), τ_2 (the probability that **Aa** transmits **A**), and τ_3 (the probability that **aa** transmits **A**). Under Mendelian transmission, $\tau_1 = 1$, $\tau_2 = {}^1/_2$, and $\tau_3 = 0$, and no transmission of the major effect is obtained when the three τ's are equal.

Hypothesis Tests

Competing models are tested for significance by using a likelihood-ratio test, which is minus twice the difference between the log-likelihood obtained under the general model (with $k + w$ parameters estimated) and the log-likelihood obtained under a reduced model (with only k of the parameters estimated). The likeli-

Table 2

Segregation Results for FM

Model	d	t	q	H	Z	τ_1	τ_2	τ_3	−2 ln L + c	AIC	χ^2 Model	χ^2
1. General Mendelian	.00	2.35	.31	.20	1.15	[1]	[1/2]	[0]	6.03	20.03		
2. No multifactorial	1.00	1.95	.09	[0]	[0]	[1]	[1/2]	[0]	14.49	24.49	2-1	8.46
3. No major	[0]	[0]	[0]	.24	.39				53.18	61.18	3-1	47.15
4. Free τ's	.00	2.32	.36	.19	.90	.78	.78	.00	.00	20.00	1-4	6.03
5. Equal τ's	.00	2.37	.06	.47	.69	.72	.72	.72	6.45	22.45	5-4	6.45
6. Constrained equal τ's[a]	.00	2.46	.25	.32	.88	[.75]	[.75]	[.75]	8.92	22.92	6-5	2.47
7. Recessive mode	[0]	2.35	.31	.20	1.15	[1]	[1/2]	[0]	6.03	18.03	7-1	.00
8. Additive mode	[1/2]	4.49	.08	.14	.67	[1]	[1/2]	[0]	12.05	24.05	8-1	6.02
9. Dominant mode	[1]	2.17	.08	.14	.69	[1]	[1/2]	[0]	9.35	22.35	9-1	3.32
10. Generation effect	.00	2.36	.30	.22	[1]	[1]	[1/2]	[0]	6.04	18.04	10-1	.01
11. Most parsimonious (d = 0, Z = 1)	[0]	2.36	.30	.22	[1]	[1]	[1/2]	[0]	6.04	16.04	11-1	.01

NOTE.—Parameters in square brackets were fixed at the values indicated.

[a] Constrained equal τ's to be in equilibrium, i.e., $\tau_1 = \tau_2 = \tau_3 = (1 - q)$.

hood ratio is distributed as a χ^2 with w df. The Akaike (1974) information criterion (AIC) can also be used in judging the fit of several alternative models. The AIC is twice the number of estimated parameters minus twice the log-likelihood, and the best model has the smallest AIC.

To infer a major gene, the following three conditions are usually required (Lalouel et al. 1983): (1) rejection of the no-major-effect hypothesis (d = t = q = 0); (2) failure to reject Mendelian transmission; and (3) rejection of no transmission of the major effect (i.e., equal τ's). If any of these conditions is not satisfied, then Mendelian transmission is rejected, and the result can be interpreted only as a nonspecified failure of the genetic model. If Mendelian τ's are supported, however, then additional tests on the major component characteristics (e.g., dominance) are conducted under the Mendelian hypothesis.

Results

The results of segregation analysis for FM are given in table 2. The hypothesis of no multifactorial effect is rejected (H = Z = 0; $\chi^2_2 = 8.46$; $P = .015$), as is the hypothesis of no major effect (d = t = q = 0; $\chi^2_3 = 47.15$; $P < .001$). Mendelian transmission is not rejected (free τ's; $\chi^2_3 = 6.03$; $P = .110$), while the equal τ's model is rejected ($\chi^2_2 = 6.45$; $P = .040$). This pattern of results satisfies all three of the requirements needed in order to claim a putative major gene for FM (Lalouel et al. 1983). Since a major gene is not ruled out, the components of the major effect are further investigated. A recessive mode of transmission (d = 0) is acceptable ($\chi^2_1 = 0.00$; $P > .999$), while an additive mode (d = 1/2) is rejected ($\chi^2_1 = 6.02$; $P = .014$). Although the dominant mode (d = 1) is not rejected ($\chi^2_1 = 3.32$; $P = .068$), the AIC suggests that the recessive mode is preferable. Finally, no generational difference in the multifactorial component (Z = 1) is detected ($\chi^2_1 = 0.01$; $P = .920$). The most parsimonious hypothesis for FM (d = 0; and Z = 1) is given in the last row of table 2. The best model includes both a multifactorial effect, accounting for 22% of the phenotypic variance, and a major recessive locus, accounting for 45% of the variance. Nine percent of the sample is in the upper distribution (i.e., $q^2 = .09$).

When equilibrium between the generations in the major component is relaxed (free and equal τ's models), the frequencies of parents and offspring in the upper distributions are no longer required to be equal. Most dramatically for FM, under the equal τ's model there are substantially fewer parents (0.42%) than offspring (7.8%) in the upper distribution. This result is consistent with the previous commingling study (Borecki et al. 1991), where parent and offspring distributions were examined separately. For FM, although only one skewed distribution was inferred in both parents and offspring, there was significant heterogeneity between the generations on the power transformation parameter, with the distribution of offspring being more skewed than that for parents. That is, there are more offspring than parents with high values. We tested an additional equal τ's model where intergenerational equi-

Table 3

Segregation Results for FFM

Model	d	t	q	H	Z	τ_1	τ_2	τ_3	−2 ln L + c	AIC	χ^2 Model	χ^2
1. General Mendelian	.13	1.47	.61	.30	.13	[1]	[1/2]	[0]	9.63	23.63		
2. No multifactorial	.40	1.93	.54	[0]	[0]	[1]	[1/2]	[0]	12.41	22.41	2-1	2.78
3. No major	[0]	[0]	[0]	.63	.79				14.24	22.24	3-1	4.61
4. No effect	[0]	[0]	[0]	[0]	[0]				66.27	70.27	4-1	56.64
5. Free τ's[a]	.47	2.16	.66	[0]	[0]	.70	.77	.01	.00	16.00	2-5	12.41
6. Equal τ's	.54	1.95	.15	[0]	[0]	.68	.68	.68	64.28	76.28	6-5	64.28
7. Constrained equal τ's[b]	.54	1.95	.32	[0]	[0]	[.68]	[.68]	[.68]	64.28	74.28	7-6	.00
8. Generation effect	[0]	[0]	[0]	.60	[1]				16.03	22.03	8-3	1.79

NOTE.—Parameters in square brackets were fixed at the values indicated.

[a] Most parsimonious by AIC.

[b] Constrained equal τ's to be in equilibrium, i.e., $\tau_1 = \tau_2 = \tau_3 = (1 - q)$.

librium is enforced in the major effect [i.e., model 6, where $\tau_1 = \tau_2 = \tau_3 = (1 - q)$]. On the basis of a likelihood-ratio test, there is no difference between the constrained and unconstrained equal τ's models ($\chi^2_1 = 2.47$; $P = .116$). These results suggest that, even though the parent and offspring distributions exhibit different levels of skewness, they are not significantly heterogeneous in their segregation patterns.

For FFM (table 3), neither the major ($\chi^2_3 = 4.61$; $P = .203$) component nor the multifactorial ($\chi^2_2 = 2.78$; $P = .249$) component is significant individually, but both cannot be dropped simultaneously ($\chi^2_5 = 56.64$; $P < .001$). Therefore, either a multifactorial-only or a major effect–only model is indicated. The major effect parameters were tested after fixing all multifactorial components to zero. Under the major effect–only model, Mendelian transmission probabilities are rejected ($\chi^2_3 = 12.41$; $P = .006$), as are equal τ's ($\chi^2_2 = 64.28$; $P < .001$), suggesting that the best hypothesis is that of free transmission probabilities. This major non-Mendelian model accounts for 59% of the variance. Under the multifactorial-only model, there is no generation difference ($\chi^2_1 = 1.79$; $P = .181$). This polygenic and/or environmentally based component accounts for 60% of the variance. However, the major non-Mendelian model (AIC = 16.00) fits the data better than does the most parsimonious multifactorial model (AIC = 22.03).

For %BF (table 4), both the major ($\chi^2_3 = 33.70$; $P < .001$) component and the multifactorial ($\chi^2_2 = 17.33$; $P < .001$) component are significant. Tests on the transmission probabilities lead to nonrejection of the Mendelian τ's ($\chi^2_3 = 5.35$; $P = .148$), while the hypothesis of equal τ's is rejected ($\chi^2_2 = 7.00$; $P = .030$). The additive mode ($\chi^2_1 = 4.90$; $P = .027$) is rejected. Although neither the dominant ($\chi^2_1 = 3.78$; $P = .052$) mode nor the recessive ($\chi^2_1 = 0.00$; $P > .999$) mode is rejected, the latter is preferred, on the basis of AIC. There is no suggestion of a generation difference in the multifactorial component ($\chi^2_1 = 1.05$; $P = .306$). As with FM, the most parsimonious model for %BF contains both a multifactorial effect (accounting for 26% of the variance) and a major Mendelian effect (accounting for 45% of the variance), with 12% of the sample in the upper distribution.

Discussion

It has long been recognized that obesity is a heterogenous phenotype, with alternative measures of obesity being differentially related to various cardiovascular risk factors (e.g., see Bouchard et al. 1990; Després et al. 1990). However, most previous genetic studies of obesity have concentrated on combination measures, such as the body-mass index (BMI), which reflect several different weight components, including fat mass, lean mass, and body composition. The current study utilizes two measures, which may be considered primary components of weight (FM and FFM), as well as a combination measure (%BF), all of which were derived from underwater weighing techniques. The distributional properties of these measures were examined elsewhere (Borecki et al. 1991), and, in the current study, we further investigate the segregation patterns. This systematic investigation of several relevant measures of body composition is undertaken with the goal of detecting, and eventually identifying and mapping, genes relevant to obesity.

Table 4

Segregation Results for %BF

Model	d	t	q	H	Z	τ_1	τ_2	τ_3	−2 ln L + c	AIC	χ^2 Model	χ^2
1. General Mendelian	.00	2.23	.34	.35	.50	[1]	[1/2]	[0]	5.35	19.35		
2. No multifactorial	.29	2.44	.30	[0]	[0]	[1]	[1/2]	[0]	22.68	32.68	2-1	17.33
3. No major	[0]	[0]	[0]	.32	2.03				39.05	47.05	3-1	33.70
4. Free τ's	.00	2.19	.37	.35	.47	.85	.65	.17	.00	20.00	1-4	5.35
5. Equal τ's	.00	2.19	.10	.67	.37	.70	.70	.70	7.00	23.00	5-4	7.00
6. Constrained equal τ's ...	.00	2.17	.30	.44	.55	[.70]	[.70]	[.70]	8.15	22.15	6-5	1.15
7. Recessive mode	[0]	2.23	.34	.35	.50	[1]	[1/2]	[0]	5.35	17.35	7-1	.00
8. Additive mode	[1/2]	4.42	.08	.27	.31	[1]	[1/2]	[0]	10.25	22.25	8-1	4.90
9. Dominant mode	[1]	2.22	.08	.29	.30	[1]	[1/2]	[0]	9.13	21.13	9-1	3.78
10. Generation effect	.00	2.19	.35	.26	[1]	[1]	[1/2]	[0]	6.40	18.40	10-1	1.05
11. Most parsimonious (d = 0, Z = 1)	[0]	2.19	.35	.26	[1]	[1]	[1/2]	[0]	6.40	16.40	11-1	1.05

NOTE.—See footnotes to table 2.

Previous commingling analyses of these variables (Borecki et al. 1991) revealed intergenerational differences in the distributions, even after adjustments for the effects of age. No commingling was detected for either of the two primary measures (FM and FFM), although there was residual skewness in the FM distributions. Consistent with the no commingling result, no evidence for a major gene was seen for FFM, which is an important component of total weight and consists primarily of bone and muscle mass. Since no skewness was indicated by commingling analysis, kurtosis is likely responsible for the major non-Mendelian effect, which may reflect environmentally based commingling or may be in part a function of gene-environment interactions or correlations, where genetic differences interact with environmental factors, such as diet and exercise. Therefore, there appears to be no evidence supporting a single gene effect influencing FFM in these data.

For FM, in which no commingling was detected, the residual skewness is unlikely to have contributed to the positive major gene result, as tests on the transmission probabilities provide a safeguard against the false inference of major genes when skewed data are analyzed (Lalouel et al. 1983; Demenais et al. 1986). Since Mendelian τ's were not rejected but equal τ's were rejected, the major gene effect remains supported. It is known that, under certain conditions (e.g., small displacements), commingled distributions may appear as a single, skewed distribution (MacLean et al. 1976), and application of a skewness transformation could diminish or remove the evidence for major genes. We further investigated this possibility by repeating the segregation analysis of FM after applying a skewness transformation (results not reported), and the major gene evidence was diminished. Specifically, after power transformation, neither the major component nor the multifactorial component was significant, given the other, although both could not be dropped simultaneously. However, under a major effect–only model, Mendelian transmission was not rejected, further supporting the evidence for a major gene.

Generational heterogeneity in the commingling patterns of FM was noted elsewhere (Borecki et al. 1991), with a greater degree of skewness in offspring distributions than in parent distributions. The generational heterogeneity was not relevant to the multifactorial component here, since the parameter Z could be fixed at 1.0. Rather, when equilibrium constraints in the major component were relaxed (free and equal τ's models), the proportions of individuals in the upper distributions were apparently different by generation, with more offspring (7.8%) than parents (0.42%). This is consistent with the commingling result. However, when equilibrium was enforced under the equal τ's model, the likelihood-ratio test suggested that the distributional difference between generations was not significant.

For the combination measure, %BF, commingling was seen only in the parent distribution, while the offspring distribution exhibited residual skewness. This generational heterogeneity may be a function of developmental effects during adolescence (Malina and Bouchard 1988), where growth is characterized by spurts

and lags, since the subjects in the offspring generation were at varying maturational stages (ages 8–25 years). Segregation analyses of %BF, after applying various transformations to reduce skewness (not reported), resulted in diminished evidence for a major gene. In general, either the multifactorial or the major components, but not both, was needed in analyses of the transformed data, and the AIC usually identified the multifactorial model as being the most parsimonious. The exception for %BF was under the least severe transformation, where the results supported a recessive major gene similar to that reported for the nontransformed phenotype.

The ratio of FM/FFM was also examined for segregation patterns. This ratio differs from %BF in that the latter would approximate fat mass proportional to total mass [FM/(FFM+FM)]. The results were not reported here since the FM/FFM ratio is highly correlated with %BF (.994 in fathers, .992 in mothers, .989 in sons, and .994 in daughters), and the segregation results were nearly identical for the two measures. The combination measures, especially the FM/FFM ratio, are indicators of the propensity to store energy as fat or lean tissue, i.e., of nutrient partitioning. Nutrient partitioning can be seen both as an indicator of body composition and as a determinant of the proneness to become obese over time. Further study is needed on these combination measures, in which repeated measures over time are incorporated so that concurrent changes in both fat measures and nutrient partitioning can be assessed under a prospective study design.

A possible confounding factor in these results is the influence of height. However, the correlations between the analysis variables and height were in general nonsignificant. The exception was for moderate correlations between FFM and height (.48 in fathers, .46 in mothers, .35 in sons, and .38 in daughters). The significance of the height-FFM correlations is not surprising, since one of the major components of lean mass is bone tissue, which is proportional to height. However, since a major gene hypothesis was not supported for FFM, further investigation of height-adjusted FFM was not undertaken. We did examine the segregation patterns of an FM index (FMI) which was adjusted for height. Those results were not reported since they were virtually identical to those for FM. This finding is not surprising, given that FM and FMI are highly correlated (.996 in fathers, .993 in mothers, .989 in sons, and .996 in daughters), with zero-order correlations between height and FM. Given these results, we conclude that height has no influence on the segregation pattern for fat mass. However, FM adjusted for height is an important measure in that it may be more closely associated with blood pressure and glucose intolerance than with other measures of body composition (C. Bouchard, unpublished data).

The major gene parameters are remarkably similar for both of FM and %BF, which are highly intercorrelated phenotypes (.90–.93). For each phenotype, the major effect accounts for about 45% of the variance, with about 9%–12% of the sample in the upper distribution. The multifactorial component is also consistent across the two measures, accounting for 22%–26% of the variance. This pattern leads us to ask whether there is a single major locus, or, alternatively, how many loci underlie both of these traits? This question warrants further investigation utilizing multivariate techniques.

Most previous segregation studies of obesity have concentrated on the BMI, which is simply computed as weight (in kg) over height (in m) squared. Clear support for a major recessive gene for BMI comes from three recent investigations (the Lipid Research Center random sample [Price et al. 1990], the Muscatine Ponderosity Study [Moll et al. 1991], and the Tecumseh Community Health Study [Province et al. 1990]). Both the Lipid Research Center and the Tecumseh studies were very large, providing the statistical power needed to detect even small effects. The Muscatine study design included a portion of the families who were ascertained through excess obesity patterns, resulting in overrepresentation of the obesity phenotype in the distributions and leading to added statistical power to detect effects. Taken together, these studies suggest a putative major recessive gene for extreme overweight (40% over ideal weight), accounting for 20%–37% of the phenotypic variance and affecting about 6% of each sample. An additional 30%–35% of the variance was attributed to polygenic and/or environmental factors. In contrast, however, examination of the BMI in our French-Canadian sample did not support a major gene effect, although a major non-Mendelian effect with additional multifactorial components could not be ruled out (Rice et al., submitted). Nor was a major gene hypothesis for BMI supported in two other studies (Karlin et al. 1981; Zonta et al. 1987). However, in our French-Canadian sample, incorporating developmental hypotheses by including genotype-specific effects of age led to support of a major recessive gene hypothesis for BMI (Borecki et al., submitted).

It is well known that the BMI is a heterogeneous phenotype that is some function of FM and FFM, as

well as body composition. In our French-Canadian sample, the correlations between BMI and FM range from .64 in sons to .83 in mothers. The correlations between BMI and FFM are somewhat lower, ranging from .54–.65, as are correlations between BMI and %BF, ranging from .46–.63 (for complete correlation table, see Borecki et al. 1991). The magnitude of these correlations, as well as the similarity of the major gene parameters for BMI, FM, and %BF, may suggest that the Mendelian signal for BMI seen in some studies may be a reflection of its more primary component; that is, it is possible that the putative major gene affecting FM may also find some expression in the BMI.

In summary, our results suggest that future genetic investigations of obesity would benefit from focusing on the relevant primary components of body composition, such as FM and %BF. These variables exhibit patterns which are consistent with segregation at a recessive major locus and with additional multifactorial effects which may be polygenic and/or cultural (environmental) in origin. A reasonable hypothesis would be to consider genes that may influence nutrient partitioning as the family of candidate genes to receive the major attention.

Acknowledgments

This work was partly supported by NIH grants GM-28719, HD-18281, HL-47317, and MH-31302, and MRC of Canada grants MA-10499 and PG-11811.

References

Akaike H (1974) A new look at the statistical model identification. IEEE Trans Automat Control AC 19:716–723

Borecki IB, Rice T, Bouchard C, Rao DC (1991) Commingling analysis of generalized body mass and composition measures: the Québec family study. Int J Obes 15:763–773

——. Single gene inheritance and the body mass index: resolution of conflicting results via evidence for genotype-dependent effects (submitted)

Bouchard C (1985) Reproducibility of body-composition and adipose-tissue measurements in humans. In: Roche AF (ed) Body-composition assessments in youth and adults: report of the sixth Ross Conference on Medical Research. Ross Labs, Columbus, Ohio, pp 9–14

Bouchard C, Pérusse L (1988) Heredity and body fat. Annu Rev Nutr 8:259–277

Bouchard C, Pérusse L, Leblanc C, Tremblay A, Thériault G (1988) Inheritance of the amount and distribution of human body fat. Int J Obes 12:205–215

Bouchard C, Savard R, Després J-P, Tremblay A, Leblanc C (1985) Body composition in adopted and biological siblings. Hum Biol 57:61–75

Burton BT, Foster WR, Hirsch J, Van Itallie TB (1985) Health implications of obesity: an NIH consensus development conference. Int J Obes 9:155–169

Demenais F, Lathrop M, Lalouel JM (1986) Robustness and power of the unified model in the analysis of quantitative measurements. Am J Hum Genet 38:228–234

Després J-P, Moorjani S, Lupien PJ, Tremblay A, Nadeau A, Bouchard C (1990) Regional distribution of body fat, plasma lipoproteins, and cardiovascular disease. Arteriosclerosis 10:497–511

Himes JH, Bouchard C (1985) Do the new Metropolitan Life Insurance weight-height tables correctly assess body frame and body fat relationships? Am J Public Health 75:1076–1079

Karlin S, Williams PT, Jensen S, Farquhar JW (1981) Genetic analysis of the Stanford LRC family study data. I. Structural exploratory data analysis of height and weight measurements. Am J Epidemiol 113:307–324

Kral JG (1985) Morbid obesity and related health risks. Ann Intern Med 103:1043–1047

Lalouel JM, Morton NE (1981) Complex segregation analysis with pointers. Hum Hered 31:312–321

Lalouel JM, Rao DC, Morton NE, Elston RC (1983) A unified model for complex segregation analysis. Am J Hum Genet 35:816–826

MacLean CJ, Morton NE, Elston RC, Yee S (1976) Skewness in commingled distributions. Biometrics 32:695–699

Malina RM, Bouchard C (1988) Subcutaenous fat distribution during growth. In: Bouchard C, Johnston FE (eds) Fat distribution during growth and later health outcomes. Alan R Liss, New York, pp 63–84

Moll PP, Burns TL, Lauer RM (1991) The genetic and environmental sources of body mass index variability: the Muscatine Ponderosity Family Study. Am J Hum Genet 49:1243–1255

Morton NE, Rao DC, Lalouel JM (1983) Methods in genetic epidemiology. Karger, Basel

Pérusse L, Rice T, Bouchard C, Vogler GP, Rao DC (1989) Cardiovascular risk factors in a French-Canadian population: resolution of genetic and familial environmental effects on blood pressure by using extensive information on environmental correlates. Am J Hum Genet 45:240–251

Price RA, Ness R, Laskarzewski P (1990) Common major gene inheritance of extreme overweight. Hum Biol 62:747–765

Province MA, Arnqvist P, Keller J, Higgins M, Rao DC (1990) Strong evidence for a major gene for obesity in the large, unselected, total Community Health Study of Tecumseh. Am J Hum Genet 47 Suppl:A143

Rice T, Borecki IB, Bouchard C, Rao DC. Segregation analysis of body mass index in an unselected French-Canadian family study: the Québec family study (submitted)

Zonta LA, Jayakar SD, Bosisio M, Galante A, Pennetti V (1987) Genetic analysis of human obesity in an Italian sample. Hum Hered 37:129–139