Segregation Analysis of Abdominal Visceral Fat: The HERITAGE Family Study

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Abstract

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A major gene hypothesis for abdominal visceral fat (AVF) level, both before and after adjustment for total body fat mass, was investigated in 86 white families who participated in the HERITAGE Family Study. In this study, sedentary families were tested for a battery of measures (baseline), endurance exercise trained for 20 weeks, and then remeasured again. The baseline measures reported here are unique in that the variance due to a potentially important environmental factor (activity level) was limited. AVF area was assessed at L4 to L5 by the use of computerized tomography scan, and total body fat mass was assessed with underwater weighing. For fat mass, a putative locus accounted for 64% of the variance, but there was no evidence of a multifactorial component (i.e., no polygenic and/or common familial environmental effects). For AVF area, both a major gene effect accounting for 54% of the variance and a multifactorial component accounting for 17% of the variance were significant. However, after AVF area was adjusted for the effects of total level of body fat, the support for a major gene was reduced. In particular, there was a major effect for fat mass–adjusted AVF area, but it was not transmitted from parents to offspring (i.e., the three transmission probabilities were equal). The importance of this study is twofold. First, these results confirm a previous study that suggested that there is a putative major locus for AVF and for total body fat mass. Second, the findings from the HERITAGE Family Study suggest that the factors underlying AVF area in sedentary families may be similar to those in the population at large, which includes both sedentary and active families. Whether the gene(s) responsible for the high levels of AVF area is the same as that which influences total body fat content remains to be further investigated.

Key words: total body fat mass, sedentary, pleiotropy

Introduction

Abdominal obesity is associated with a complex of disturbances known as the metabolic syndrome (3) that includes a greater susceptibility to glucose intolerance, insulin resistance, and compensatory hyperinsulinemia (12,14,19); a less favorable and potentially atherogenic plasma lipid and lipoprotein profile (10,11); and elevated blood pressure (13). To understand how these metabolic disturbances are related at the causal level involves understanding the etiological basis of each trait. The genetic and common environmental factors leading to abdominal obesity, specifically abdominal visceral obesity, constitute the emphasis of this article.

The first suggestion of a genetic component for abdominal visceral fat (AVF) level came from intervention studies conducted with identical twins. The within-pair variability for changes in AVF area in response to an extended period of overfeeding (8) and negative energy balance (7) was significantly lower than the among-pair variability, suggesting a genetic basis for the propensity to store or mobilize fat in the visceral area. The only other report of familial factors underlying AVF area came from the Québec Family Study (QFS). The maximal heritability for AVF area, unadjusted and adjusted for total fat mass, was 58%

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and 56%, respectively (20). Also, evidence consistent with a major gene accounting for 51% of the variance and additional familial multifactorial effects accounting for 21% of the variance was found in the QFS (6).

In the HERITAGE Family Study, the genetic and nongenetic determinants of the response to endurance exercise training for several cardiovascular risk factors in sedentary families are investigated. A battery of measures relating to cardiovascular risk was collected both before (baseline) and after a 20-week endurance exercise training regimen. The baseline measures for families in this study are unique, in that a potentially powerful environmental source of familial variance (activity levels) are controlled for. The primary aim of this study is to confirm (1) whether there is evidence for a putative major gene in the HERITAGE families, and (2) if so, how it may compare with that found in the QFS.

Methods and Procedures

Sample

The HERITAGE sample and study protocol are more thoroughly outlined elsewhere (5). In summary, 98 nuclear, white families, each with both biological parents and at least two biological children, will have completed the exercise training protocol. This study includes complete data on 86 families. Exact sample sizes for fathers, mothers, sons, and daughters are given in Table 1. Families of African-American descent were also recruited but are not reported in here. Recruitment of families was based on extensive publicity and advertisements from four clinical centers.

Several criteria were used to screen subjects for participation. First, individuals were required to be between the ages of 16 years and 65 years (16 years to 40 years for children and 65 years or less for parents) in order to avoid maturation (low end) and aging (high end) complications. Second, individuals were required to be in good health in order to complete the maximal exercise training. Third, families were required to be sedentary, defined at baseline as no regular physical activity over the previous 6 months, i.e., any activity lasting 30 minutes or more, involving an energy expenditure of at least 7 METS (1 MET equals 3.5 mL of O_2 uptake per kg bodyweight per min) in individuals $\geq$50 years or 8 METS for younger individuals, and occurring more than once a week. Families with some nonsedentary members were included provided that the nonsedentary individual(s) remained inactive for at least 6 months. Fourth, individuals with a body mass index (BMI) of more than 40 kg/m^2 were usually excluded because of metabolic abnormalities and exercise difficulties associated with extreme obesity, unless certified by a physician. Fifth, individuals with blood pressures higher than 159 mm Hg for systolic and/or 99 mm Hg for diastolic were also excluded. Finally, individuals with any condition or disease that is life-threatening or that could be aggravated by cycle exercise were excluded. For example, definite or possible coronary heart disease and chronic or recurrent respiratory problems were bases for exclusion, as were uncontrolled endocrine and metabolic disorders, including diabetes or use of lipid-lowering drugs. See Bouchard et al. (5) for a detailed list of exclusionary criteria.

Measures

Each individual was examined on a battery of measures both before (baseline) and after completing a 20-week standardized training program. Only the baseline measures are investigated here. AVF was assessed by use of a computerized tomography scan. Subjects were examined in the supine position with their arms stretched above the head (23), and the abdominal scan was obtained between the fourth and fifth lumbar vertebrae. The attenuation interval used in the quantification of the areas of adipose tissue was from −190 Hounsfield units to −30 Hounsfield units. The AVF area was defined by drawing a line within the muscle wall surrounding the abdominal cavity. This area is primarily located in the adipose tissue of the abdominal cavity and is referred to here as the AVF area. Underwater weighing was performed to determine fat mass (2), and a correction was made for residual lung volume by the oxygen dilution method (25,26).

Means and standard deviations for the raw (unadjusted) AVF in cm^2 of area at L4 to L5, raw fat mass (kg), and age (years) are given in Table 1, separately in four sex by generation groups (fathers, mothers, sons, and daughters). On

Table 1. Sample statistics for AVF and fat mass (FM)

	Fathers			Mothers			Sons			Daughters		
Variable	**n**	**Mean**	**SD**	**n**	**Mean**	**SD**	**n**	**Mean**	**SD**	**n**	**Mean**	**SD**
Age (years)	86	52.9	5.2	85	41.7	5.2	128	24.7	5.9	138	24.3	5.9
AVF (cm^2)	86	159.2	57.2	85	121.0	59.9	127	74.9	41.7	135	48.6	26.3
FM (kg)	84	25.0	9.0	82	27.5	10.4	123	16.6	10.6	138	17.1	9.1
BMI (kg/m^2)	86	28.4	4.3	86	27.5	4.9	127	25.5	4.7	138	25.8	8.7

the basis of a comparison of standard errors, there appear to be significant generation differences within each sex for AVF area and for fat mass, with higher levels in parents. There are significant sex differences for AVF area, with higher levels in boys/men within each generation. However, sex differences for fat mass are significant only in parents (higher in mothers), with approximately equal levels in sons and daughters. For comparison purposes, the means and standard deviations for BMI are also given in Table 1.

Age Adjustments

AVF and fat mass were adjusted for the effects of baseline age, separately within each of the four sex by generation groups (fathers, mothers, sons, daughters), by use of a stepwise multiple regression procedure. In summary, a given measure was regressed on a polynomial in age (linear, quadratic, and cubic) in a stepwise manner, retaining only those terms that were significant at the 5% level. Thus, the residual score from this regression stands corrected for age, sex, and generation effects. For fat mass, age was a significant predictor in each of the fathers (age^3 term accounting for 1.96% of the variance), mothers (age^3 accounting for 3.52%), sons (age and age^3 terms accounting for 21.77%), and daughters (age term accounting for 6.44%). Age was also a significant predictor for AVF in each group (linear term in age accounting for 6.83% in fathers, age^3 accounting for 5.74% in mothers, age and age^3 accounting for 29.81% in sons, and age^3 accounting for 15.03% in daughters). The AVF and fat mass phenotypes used in the genetic analysis were defined as the age-adjusted and standardized residual scores (with zero mean and unit variance in each sex by generation group) from these regression analyses.

A similar set of stepwise regressions (by sex and generation groups) was performed on AVF area by using polynomials in age (age, age^2, and age^3) and fat mass (FM, FM^2, and FM^3). Fat mass accounted for a larger percentage of variance in AVF than did age. In summary, 42.61% of the variance in fathers was due to both age and fat mass terms (age, FM, FM^2), 48.04% in mothers (age, FM), 68.22% in sons (age^3, FM), and 62.62% in daughters (age^3, FM). The FM-adjusted AVF phenotype used in the genetic analysis was defined as the age and fat-mass adjusted and standardized residual score from these regression analyses.

Commingling

The method of commingling analysis as described in MacLean et al. (17) and implemented in the computer program SKUMIX (18) was used. A mixture of up to three distributions in Hardy-Weinberg proportions can be fitted, optionally including p, the power transformation parameter. There are five parameters in the model in addition to p: the common variance in each component (E); the overall mean (u); the gene frequency (q), which determines the relative proportion of the component distribution with the highest mean (q^2) under the assumption of Hardy-Weinberg proportions; the displacement between the two extreme component means (t); and the relative position of the mean of the middle component (d). Parameters were estimated by the method of maximum likelihood, and tests of hypotheses for nested models were carried out using the likelihood ratio test. The test criterion, which is the difference in the log-likelihoods (-2 ln L) obtained under two models, is distributed asymptotically as a χ^2, with the degrees of freedom being equal to the difference in the number of parameters estimated in the competing models. Nonnested models are compared by use of Akaike's (1) Information Criterion (AIC), which is -2 ln L plus twice the number of estimated parameters, and the "best" model is the one with the smallest AIC.

Segregation Model

Segregation analysis was carried out using the unified mixed model (15) as implemented in the computer program POINTER (16–18). The model assumes that a phenotype is composed of the independent and additive contributions from a major effect, a heritable multifactorial background, and a unique environmental residual. The major effect is assumed to result from the segregation at a single locus having two alleles (i.e., A and a). The A allele is defined as decreasing the quantitative phenotype. There are seven parameters in the model: the overall variance (V); the overall mean (u), the major locus gene frequency (q); the displacements between the two homozygous means (t), the relative position of the heterozygous mean, or dominance (d); and the multifactorial heritability in offspring (H) and in parents (HZ). The transmission pattern of the major gene from parents to offspring is characterized by three parameters: τ_1 is the probability that an AA individual transmits allele A to the offspring; τ_2 is the probability that Aa transmits A; and τ_3 is 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 values are equal. To infer a major gene, three conditions are usually required (16): (1) rejection of the no major effect hypothesis ($q = t = d = 0$); (2) failure to reject Mendelian transmission; and (3) rejection of the no transmission model (equal τ values). Competing models are tested for significance by use of the likelihood ratio test.

Results

Commingling Analysis

The commingling results for fat mass suggested that the best model consists of three normal distributions, as depicted in Figure 1 (superimposed on the frequency distribution). The component distributions are represented by dashed lines, with the solid line characterizing the overall

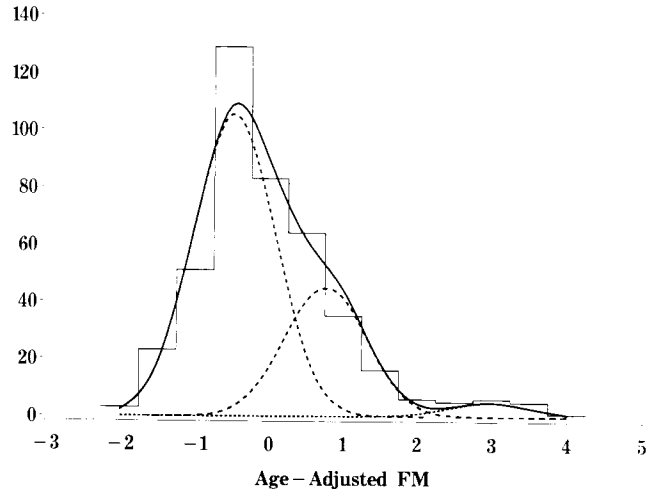

Figure 1: Histogram of fat mass, with most parsimonious commingling model (three normal distributions) superimposed: $E = 0.29942$, $u = -0.01101$, $d = 0.35902$, $t = 3.45573$, $q = 0.17675$, $p = 1.0$. The dotted lines represent the component distributions, and the solid line characterizes the overall distribution. The x axis represents age-adjusted fat mass, with the y axis denoting the frequency.

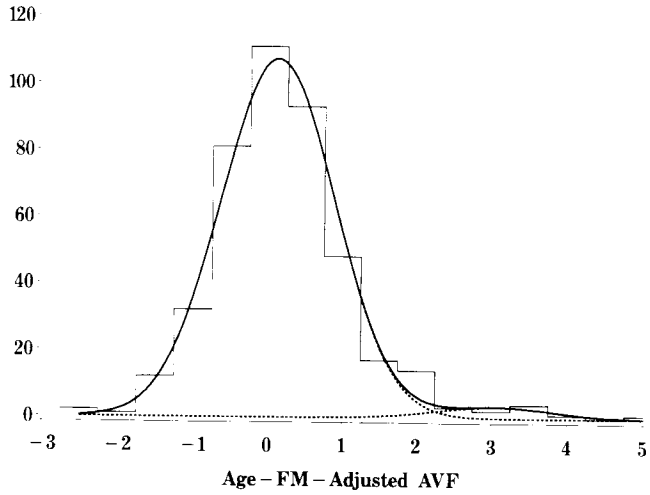

Figure 3: Histogram of fat mass–adjusted AVF, with most parsimonious commingling model (two normal distributions) superimposed: $E = 0.57497$, $u = -0.21110$, $d = 0$, $t = 2.92124$, $q = 0.17436$, $p = 1.0$. The dotted lines represent the component distributions, and the solid line characterizes the overall distribution. The x axis represents age-fat mass-adjusted AVF area, with the y axis denoting the frequency.

distribution. For AVF area, the best model corresponds to a commingling of three skewed distributions, which is depicted in Figure 2. For fat mass–adjusted AVF, two normal distributions best characterized the data. The two-normal distribution model is shown in Figure 3. The finding of multiple distributions is compatible with a major gene hypothesis, although not considered prima facie evidence because commingling can arise through other causes. Segregation analysis was used to determine if these major effects segregated in families according to Mendelian expectations.

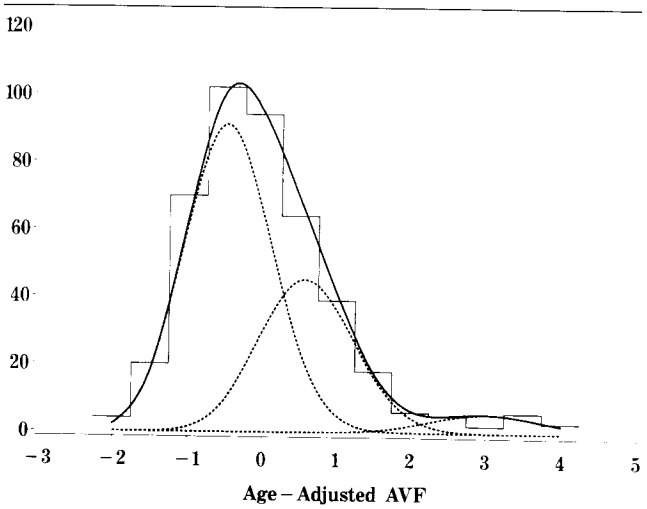

Figure 2: Histogram of AVF area, with most parsimonious commingling model (three skewed distributions) superimposed: $E = 0.37027$, $u = -0.03593$, $d = 0.32774$, $t = 3.22738$, $q = 0.19880$, $p = 0.54656$. The dotted lines represent the component distributions, and the solid line characterizes the overall distribution. The x axis represents age-adjusted AVF area, with the y axis denoting the frequency.

Segregation Analysis

A summary of the log-likelihoods for the segregation analysis is given in Table 2. For fat mass, the major effect was significant (model 3–model 1: $\chi^2_3 = 78.83$, $p<0.001$), but the multifactorial component was not (model 2–model 1: $\chi^2_2 = 3.98$, $p = 0.137$). None of the recessive (model 6–model 1: $\chi^2_1 = 14.67$, $p<0.001$), codominant (model 7–model 1: $\chi^2_1 = 37.36$, $p<0.001$) or dominant (model 8–model 1: $\chi^2_1 = 34.41$, $p<0.001$) modes of inheritance fit the data. The transmission probabilities were tested under the parsimonious Mendelian model (no multifactorial inheritance), and all of the conditions needed to satisfy a major gene hypothesis were met: (1) the major effect was significant (model 3–model 1: $\chi^2_3 = 78.83$, $p<0.001$); (2) the hypothesis of Mendelian τ values was not rejected (model 9–model 12: $\chi^2_3 = 4.23$, $p = 0.238$); and (3) the equal τ values hypothesis was rejected (model 11–model 12: $\chi^2_3 = 46.695$, $p<0.001$). The parameter estimates for this Mendelian model are given in Table 3. The putative major gene accounted for 64% of the phenotypic variance and affected 6% (q^2) of the sample.

Table 2. Segregation analysis log-likelihoods*

Model	FM	AVF	AVF-FM
Model			
1. General Mendelian	0.248	3.745	6.780
2. No Multifactorial Effect (H=Z=0)	4.228	14.310	29.806
3. No Major Effect (d=t=q=0)	79.075	76.813	42.109
4. No Effect (d=t=q=H=Z=0)	135.670	110.606	78.967
5. No Generation Difference (Z=1)	2.637	4.389	8.205
6. Recessive (d=0)	14.922	5.828	9.894
7. Codominant (d=1/2)	37.606	23.162	35.421
8. Dominant (d=1)	34.662	24.873	37.325
Parsimonius Mendelian Model			
9. H=Z=0	4.228		
10. d=0, Z=1		6.133	10.429
Tests on Transmission Probabilities			
11. Equal τ Values (τ_1=τ_2=τ_3=1−q)	46.695	8.315	4.705
12. General Transmission (Free τ Values)	0.000	0.000	0.000

*The likelihood values were scaled by subtracting the following values from each model: 603.008 for fat mass (FM), 630.910 for AVF, and 584.451 for AVF-FM

For AVF area (Table 2), both of the major (model 3–model 1: χ^2_3=73.07, p<0.001) and multifactorial components were significant (model 2–model 1: χ^2_2=10.57, p=0.005). The recessive mode of inheritance fit the data (model 6–model 1: χ^2_1=2.08, p=0.149), but the codominant (model 7–model 1: χ^2_1=19.42, p<0.001) and dominant (model 8–model 1: χ^2_1=21.09, p<0.001) modes did not. No generation difference in the multifactorial effect was found (model 5–model 1: χ^2_1=0.64, p=0.422). The transmission probabilities were tested under the parsimonious Mendelian model (hypothesis 10: no generation difference in the multifactorial component and a recessive mode of inheritance for the major gene component), and all of the conditions needed to satisfy a major gene hypothesis were met: (1) the major effect was significant (model 3–model 1: χ^2_3=73.07, p<0.001); (2) the hypothesis of Mendelian τ values was not rejected (model 10–model 12: χ^2_3=6.13, p=0.105); and (3) the equal τ value hypothesis was rejected (model 11–model 12: χ^2_3=8.32, p=0.040). The parameter estimates under this Mendelian model are given in Table 3. The putative major gene accounted for 54% of the variance and affected 8% (q^2) of the sample, and an additional 17% of the variance was accounted for by a multifactorial effect.

For fat mass–adjusted AVF (Table 2), both of the major (model 3–model 1: χ^2_3=35.33, p<0.001) and multifactorial components were significant (model 2–model 1: χ^2_2=23.03, p<0.001). The recessive mode of inheritance fit the data (model 6–model 1: χ^2_1=3.11, p=0.078), but the codominant (model 7–model 1: χ^2_1=28.64, p<0.001) and dominant (model 8–model 1: χ^2_1=30.55, p<0.001) modes did not. No generation difference in the multifactorial effect was found (χ^2_1=1.43, p=0.233). The transmission probabilities were tested under the parsimonious Mendelian model (hypothesis 10: no generation difference in the multifactorial component and a recessive mode of inheritance for the major gene component). Although the major effect was significant (model 3–model 1: χ^2_3=35.33, p<0.001), the τ values were not Mendelian (model 10–model 12: χ^2_3=10.43, p=0.015), and the equal τ value hypothesis was not rejected (model 11–model 12: χ^2_3=4.71, p=0.195). Thus, although there was a major effect, it was not transmitted according to Mendelian expectations. The parameter estimates under this non-Mendelian model are given in Table 3. The major non-Mendelian effect accounted for 28% of the variance, and an additional 42% of the variance was due to a multifactorial effect.

Discussion

There was a dual interest in this investigation of baseline AVF in the HERITAGE Family Study. First, we wished to understand if the segregation patterns in these sedentary families were consistent with a major gene hypothesis. Second, we wished to gain a better understanding of how these inactive families compared with a more heterogeneous population, because the variation due to a plausible environmental factor, physical activity, was limited in the HERITAGE study design.

Major gene studies for total fat mass or AVF area are few. In fact, only two segregation studies for fat mass (9,21), and only one study for AVF (6) have been noted. In Rice et al. (21) and Bouchard et al. (6), the sample consisted of French Canadians who are participating in the QFS. In Comuzzie et al. (9), the sample consisted of Mexican-American families participating in the San Antonio Family Heart Study. Both studies are presumed to include both sedentary and active families.

The segregation patterns resulting from these studies are reviewed in Table 4. For fat mass, each of the QFS, San Antonio, and HERITAGE studies is consistent in suggest-

Table 3. Most parsimonious segregation models ($Z=1$)

Variable	V	u	d	t	q	H
FM*	0.91 ± 0.09	−0.03 ± 0.06	0.25 ± 0.02	3.17 ± 0.12	0.24 ± 0.03	[0]
AVF*	1.11 ± 0.85	0.06 ± 0.07	[0]	2.86 ± 0.19	0.28 ± 0.03	0.17 ± 0.03
AVF-FM†	0.75 ± 0.06	0.23 ± 0.08	[0]	2.18 ± 0.20	0.22 ± 0.03	0.42 ± 0.06

*Mendelian transmission ($\tau_1=1$, $\tau_2=1/2$, $\tau_3=0$). FM, fat mass
†No transmission of major effect (i.e., equal τ values: $\tau_1=\tau_2=\tau_3=1-q=0.78$)

ing that there is a major gene effect accounting for an appreciable percentage of the variance (between 37% and 64%). The major differences among studies are that in San Antonio, there were sex-specific effects in the segregation patterns, and in the HERITAGE, there was no evidence for a multifactorial effect. Together, these three studies suggest that for fat mass, there may be some differences across populations. In particular, the percentage of variance due to the putative locus is higher in the HERITAGE study (64% as compared with 45% in the QFS), whereas that due to the multifactorial component is larger in the QFS (26% vs. 0% in the HERITAGE study). This is exactly the pattern of predicted results if (1) fat mass is determined by a major gene that is modified by environmental factors, and (2) physical activity represents that environmental factor, which is controlled to a large extent in the HERITAGE study but not in the QFS. This implies that an active lifestyle has an effect on total fat mass.

For AVF area, the results from the QFS and HERITAGE studies are remarkably consistent, suggesting a putative major gene accounting for between 51% and 54% of the variance, and a multifactorial effect accounting for an additional 17% to 21% of the variance. Thus, the familial basis for the amount of fat in the abdominal visceral area may be more homogeneous across the studies reviewed because little difference in pattern or magnitude was noted. This comparison suggests the possibility that a moderately active lifestyle may not greatly affect the amount of AVF, that members of the QFS population are, for the most part, sedentary, or both.

The results across the QFS and the HERITAGE studies were also consistent in that there was reduced evidence for a putative major gene in AVF area after it was adjusted for total body fat levels. If only a single locus determined both fat mass and AVF levels, one might expect the major effect to disappear for the residual AVF (i.e., fat mass adjusted). However, the major effect was significant, albeit non-Mendelian, perhaps suggesting the hypothesis of multiple underlying major factors. For example, a single major locus may underlie both traits (i.e., pleiotropy), with either or both traits also influenced by a different major gene as well (i.e., oligogenic). The non-Mendelian nature of this second locus may be the result of unmodeled genotype-specific covariate effects, or it may be environmental in origin. In support of multiple underlying determinants, familial clustering in the multifactorial component was found previously for fat mass and AVF area in the QFS (22). There were significant common causes for the covariation between fat mass and AVF

Table 4. Percentages of variance accounted for by genetic and/or environmental effects

Study	Variable	Major Gene (%)	Multifactorial Effect (%)	Total Variance (%)
Rice et al. (21)	FM*	45	26	71
Comuzzie et al. (9)	FM-males†	37	18	55
	FM-females†	43	35	78
Rice et al.‡	FM*	64	0	64
Bouchard et al. (6)	AVF	51	21	72
Rice et al.‡	AVF	54	17	71

*or % body fat. From underwater weighing
†From bioelectric impedance
‡This study

level (accounting for about 43% of the common variance), as well as additional significant familial effects specific to each trait (as much as 20% of the variance in each), with the common etiology involving complex interactions with both sex and age (i.e., generation).

In summary, the results for total body fat are consistent with a gene-by-environment interaction hypothesis. That is, the effect of the major locus on fat mass may be modified by environmental factors such as activity level. The results also suggest an oligogenic-pleiotropic model underlying fat mass and AVF area. That is, a major gene may underlie both traits (pleiotropy), and there may be additional familial factors that are specific to each trait (oligogenic). Furthermore, the pleiotropic effect may involve genotype-dependent effects of age and/or sex. Whether the familial effects underlying each of the traits are due to major genes, polygenes, familial environmental factors, or some combination can be tested by the use of more complex bivariate segregation methods (e.g., Ref. 4). In support of the pleiotropic hypothesis, one locus on mouse chromosome 9, which was identified by the quantitative trait locus mapping method applied to a crossbreeding experiment between mouse strains resistant to (SWR/J) and sensitive to (AKR/J) high-fat diets, was found to influence both total adiposity (7% of the variance) and mesenteric adipose tissue mass (47% of the variance) (24). In addition, whether AVF shares common genetic etiologies with outcome variables of the metabolic syndrome such as hypertension, glucose intolerance, hyperinsulinemia, or dyslipoproteinemia also warrants further investigation. The results of these studies should help us understand why some individuals become viscerally obese and thus more at risk for metabolic complications, whereas others do not, and eventually provide us with the molecular tools to identify the high-risk cases.

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