Familial Resemblance for Body Composition Measures: The HERITAGE Family Study

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Abstract

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A sex-specific familial correlation model was used to assess the heritable contributions to several measures of body composition in 86 sedentary white families participating in the HERITAGE Family Study. For this study, sedentary families were recruited, tested for a battery of measures, endurance exercise trained for 20 weeks, and remeasured. This sample is unique in that activity level was controlled for in these families at baseline measurement. In this report, three body composition variables measured at baseline were analyzed, two indexing adiposity (total subcutaneous fat based on eight skinfold measurements [SF8] and percent body fat measured by underwater weighing techniques [%BF]) and one assessing fat free mass ([FFM] derived from underwater weighing). The maximal heritabilities for SF8 (34%) and %BF (62%) were consistent with those reported in previous studies. There were no sex nor generation differences in the familial correlations, and the spouse correlation was significant, consistent with the hypothesis that the familial aggregation reflects genetic and familial environmental factors. However, the results for FFM were very different. The most parsimonious pattern of familial resemblance was consistent with mitochondrial inheritance (i.e., mother-offspring and sibling correlations were equal and were larger than those for spouse and father-offspring pairs). Under the mitochondrial hypothesis, 39% of the variance was accounted for by familial/genetic effects. However, under a nonmitochondrial hypothesis, which could not be ruled out, 65% of the FFM phenotypic variance was accounted for by familial/genetic factors. This high heritability level, as compared with results from previous studies, is consistent with the hypothesis that activity may constitute an important environmental determinant of FFM. These alternative hypotheses for FFM warrant further investigation using complex multilocus-multitrait segregation models, which allow for major genetic, polygenic, and environmental sources of variance, as well as interactions among them.

Key words: mitochondrial inheritance, sedentary families

Introduction

It is known that there are familial causes underlying the variation in body composition (5,8,14,15,18,19) and that the relative effect of genes vs. family environments varies, depending on the particular measure of body composition. For example, the family environment is considered to be the primary source of familial resemblance for total subcutaneous fat, accounting for about 30% of the variance (see Ref. 5). Of the total accountable variance for percent body fat (%BF: 55%), over half (30%) was attributed to familial environmental factors, whereas for fat free mass (FFM), a larger percentage was due to genes (30%) than environments (10%). In addition to these main effects of genes and environments, overfeeding (7) and exercise training (6) experiments with monozygotic (MZ) twins provide evidence for gene-by-environment interactions on body composition. In those studies, the MZ within-pair variability for changes in body composition was lower than the among-pair variability, suggesting that individuals with the same genotype respond more similarly than do unrelated individuals to the same environmental stimuli.

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One potentially powerful environmental factor influencing body composition is energy expenditure from physical activity. Therefore, studies of sedentary families should provide a more controlled environmental condition for investigating the sources of familial variance for body composition measures. By contrasting the findings in sedentary families with those previously reported in the literature, which presumably include both active and inactive families, new information concerning the roles of genes and gene-by-environment interactions may be learned. In this study, the familial aggregation of three body composition measures was examined in the HERITAGE families, in which one of the most important recruitment criteria was that all family members were sedentary at baseline. The three body composition variables measured here include an index of total subcutaneous fat (sum of eight skinfolds), %BF, and FFM; the latter two variables were assessed using the underwater weighing technique.

Methods and Procedures

Sample

The HERITAGE Family Study design and protocol are more thoroughly outlined elsewhere (4). A total of 98 nuclear families of Caucasian descent, each with both biological parents and at least three biological children, were recruited. In this study, 86 families have completed the protocol; sample sizes for fathers, mothers, sons, and daughters are given in Table 1. In addition, families of African-American descent were recruited but are not reported here. Recruitment was based on extensive publicity and advertisements from four clinical centers and included the following criteria. 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, all subjects were required to be sedentary, defined at baseline as engaging in no regular physical activity over the previous 6 months. Regular physical activity was assessed by a physician at the screening interview and was defined as any activity lasting 30 minutes or more and involving an energy expenditure of at least 7 METS (1 MET is 3.5 mL of O_2 uptake per kg bodyweight per minute) in individuals >50 years or at least 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, and verification of inactivity after 6 months was monitored by the physician. Only six individuals were in this latter group. A third criterion was that individuals with a body mass index (BMI) greater than 40 kg/m^2 were usually excluded because of metabolic abnormalities and exercise difficulties associated with obesity, unless certified by a physician. Fourth, individuals were excluded if their blood pressures were greater than 159 mm Hg for systolic and/or greater than 99 mm Hg for diastolic. Finally, individuals were required to be in good health in order to complete the exercise training. Therefore, 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 reasons for exclusion, as were uncontrolled endocrine and metabolic disorders, including diabetes or use of lipid-lowering drugs.

Measures

Each individual was given a battery of measures both before (baseline) and after a 20-week standardized exercise training program. Only the baseline measures for three body composition variables are reported here. The sum of eight skinfolds (SF8) assessed the overall level of subcutaneous fat. The eight skinfolds (subscapular, suprailiac, abdominal, midaxillary, triceps, biceps, medial calf, and thigh) were

Table 1. Sample statistics

Variable	n	Mean	SD	n	Mean	SD
		Fathers			Mothers	
Age (years)	84	52.86	5.21	82	51.52	5.02
SF8 (mm)	76	148.18	51.02	74	196.22	53.17
%BF (kg)	84	27.72	6.32	82	36.95	7.75
FFM (kg)	84	62.83	7.45	82	44.68	4.98
		Sons			Daughters	
Age (years)	123	24.61	5.89	138	24.34	5.95
SF8 (mm)	122	119.41	52.40	135	142.89	47.54
%BF (kg)	123	19.10	8.88	138	25.81	8.68
FFM (kg)	123	64.97	7.81	138	45.81	5.32

measured with Harpenden calipers (11), and each was based on the mean of two trials. A third trial was administered if the difference between the first two was not within 1.0 mm. Underwater weighing was used to determine total body fat mass and FFM (2), with a correction made for residual lung volume assessed by the oxygen dilution method (20,22). At the Laval University Clinical Center, residual lung volume was assessed by use of the helium dilution technique (12,13). The %BF and FFM in kilograms were calculated and used in this study. A detailed explanation of the underwater weighing method is found elsewhere (Ref. 21 and *Manual of Operating Procedures* available from Laval University).

Age Adjustments

Each of the body composition measures was adjusted for baseline age. A given measure was regressed on a polynomial in age in a stepwise manner, separately in each of four sex-by-generation groups (fathers, mothers, sons, and daughters). Only the terms that were significant at the 5% level were retained. The age-adjusted and standardized residuals resulting from these regressions were used as the phenotypes in the familial analyses. Table 2 gives the significant age terms and the percentages of variance accounted for. In general, age accounted for more variance in the body composition of offspring than of parents.

Familial Correlation Model

Familial correlations were used to assess the degree of familial resemblance for these measures. In summary, four individuals (fathers [f], mothers [m], sons [s], and daughters [d]) led to eight correlations within three familial classes (one spouse [fm], four parent-offspring [fs, fd, ms, md], and three sibling [ss, dd, sd]). The maximum-likelihood computer program SEGPATH (16) was used to fit the model directly to the family data under the assumption that the phenotypes in the family jointly follow a multivariate normal distribution. A general model and several null hypotheses were estimated. Null hypotheses were tested using the likelihood ratio test (the difference in minus twice the log likelihoods [−2 ln L] obtained under two models), which is distributed approximately as a χ^2 with the degrees of freedom being the difference in the number of parameters estimated in the two models. Each null hypothesis was compared with the general model for these likelihood ratio tests. Non-nested models were compared using 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.

The null hypotheses included several tests of sex and generation differences. The general model (all eight correlations) was estimated in hypothesis 1. In hypothesis 2, there were no sex differences allowed in offspring (i.e., fs = fd, ms = md, ss = dd = sd, $df = 4$). No sex differences in offspring or parents were allowed in hypothesis 3 (i.e., fs = fd = ms = md, ss = dd = sd, $df = 5$). In hypothesis 4, no sex or generation differences were allowed (i.e., fs = fd = ms = md = ss = dd = sd, $df = 6$). In hypothesis 5, a mitochondrial pattern of inheritance was tested by equating all mother-child and sibling correlations (i.e., ms = md = ss = dd = sd, $df = 4$), with no constraints on the spouse and father-child correlations. In hypothesis 6, all of the correlations were equated (i.e., fm = fs = fd = ms = md = ss = dd = sd, $df = 7$). The significance of the correlations was tested by familial class in the remaining hypotheses. In hypothesis 7, no sibling correlations were allowed (i.e., ss = dd = sd = 0, $df = 3$). There were no parent-offspring correlations in hypothesis 8 (i.e., fs = fd = ms = md = 0, $df = 4$), and there was no spouse correlation in hypothesis 9 (i.e., fm = 0, $df = 1$). Finally, no familial resemblance at all was tested in hypothesis 10 by fixing all of the correlations to zero (i.e., fm = fs = fd = ms = md = ss = dd = sd = 0, $df = 8$). The most parsimonious model was derived by combining all nonrejected hypotheses.

Table 2. Age adjustments—significant terms (percent variance accounted for)

Variable	Fathers	Mothers	Sons	Daughters
SF8	None	None	Age (22.22%)	None
%BF	None	Age[3] (6.89%)	Age (23.39%)	Age (7.48%)
FFM	None	None	Age (4.83%)	None

A polynomial in age (age, age^2 and age^3) was used in a stepwise regression, retaining only those terms that were significant at the 0.05 level.

Results

Table 3 gives the model fitting results. For SF8, none of the sex and/or generation differences tests were rejected: there were no sex differences in offspring (hypothesis 2: $p = 0.535$); no sex differences in parents or offspring (hypothesis 3: $p = 0.511$); no sex or generation differences (hypothesis 4: $p = 0.601$); the mitochondrial hypothesis was not rejected (hypothesis 5: $p = 0.766$); and all of the correlations could be equated (hypothesis 6: $p = 0.713$). The sibling (hypothesis 7: $p = 0.015$) and parent-offspring correlations (hypothesis 8: $p = 0.021$) were significant, but the spouse correlation was not (hypothesis 9: $p = 0.154$). The parsimonious model for SF8 combined the hypotheses of no spouse correlation and no sex or generation differences (hypotheses 4 and 9), i.e., a single correlation representing parent-

Table 3. Model fitting results

Null hypothesis*	df	SF8 χ^2	SF8 p	SF8 AIC	%BF χ^2	%BF p	%BF AIC	FFM χ^2	FFM p	FFM AIC
1. General				16.00			16.00			16.00
2. No sex differences in offspring	4	3.14	0.535	11.14	0.60	0.963	8.60	3.00	0.559	11.00
3. No sex differences in parents or offspring	5	4.27	0.511	10.27	0.66	0.985	6.66	4.91	0.427	10.91
4. No sex nor generation differences	6	4.57	0.601	8.57	0.99	0.986	4.99	11.08	0.086	15.08
5. Mitochondrial inheritance	4	1.83	0.766	9.83	1.71	0.789	9.71	2.31	0.680	10.31
6. Equal correlations	7	4.57	0.713	6.57	1.10	0.993	3.10	13.47	0.062	15.47
7. No sibling correlations	3	10.55	0.015	20.55	37.95	<0.001	47.95	50.15	<0.001	60.15
8. No parent-offspring correlations	5	11.60	0.021	19.60	32.02	<0.001	40.02	28.21	<0.001	36.21
9. No spouse correlation	1	2.04	0.154	16.04	13.58	<0.001	27.58	1.66	0.197	15.66
10. No correlations	8	25.24	0.001	25.24	81.43	<0.001	81.43	77.16	<0.001	77.16
11. Most parsimonious										
(4), (9)	7	7.23	0.406	9.23						
(6)	7	4.57	0.713	6.57	1.10	0.993	3.10			
(5), (9)	5							4.56	0.472	10.56

*See text for specific parameter reductions under each null hypothesis.

offspring and sibling resemblance. The test for this combined hypothesis was not rejected ($\chi^2_7 = 7.23$, $p = 0.406$, AIC = 9.23). However, the AIC suggested that the model in which all eight correlations were equated, including the spouse correlation (hypothesis 6), provided a better fit (AIC = 6.57). The latter hypothesis was chosen as the most parsimonious model for SF8.

For %BF, none of the sex differences models were rejected in hypotheses 2 through 6, and each of the sibling, parent-offspring, and spouse correlations were significantly different from zero in hypotheses 7 through 9 ($p<0.001$ for each). The most parsimonious model was hypothesis 6, in which all correlations were equated (AIC = 3.10).

For FFM, none of the sex differences models were rejected (hypotheses 2 through 6). From among these alternative models, the mitochondrial hypothesis provided the best fit by AIC (10.31). The sibling and parent-offspring correlations were significant ($p<0.001$ for each), but the spouse correlation was not ($p = 0.197$). The combined test of mitochondrial inheritance (hypothesis 5) and no spouse resemblance (hypothesis 9) was not rejected ($\chi^2_5 = 4.56$, $p = 0.472$, AIC = 10.56).

Table 4 gives the parameter estimates (± standard errors) under the general and most parsimonious models for each of the body composition measures. The maximal heritabilities are given in the last row of Table 4. These estimates of 34% and 62% for SF8 and %BF, respectively, include both genetic and familial environmental sources of variance and are adjusted for the degree of spouse resemblance. For FFM, the maximal heritability estimate of 65% is simply twice the average familial correlation, because parent-offspring and sibling pairs share half of their genes in common. The nonsignificant spouse correlation is consistent with a purely genetic etiology. However, under mitochondrial inheritance, mother-offspring and sibling pairs share 100% of their mitochondrial DNA, and the maximal heritability is simply the average of the mother-offspring and sibling correlations. Under this hypothesis, there is additional sex-specific father-child resemblance.

Discussion

In this study, a sex-specific familial correlation model was used to assess the heritable contributions for three measures of body composition in sedentary families. The sedentary nature of these families provides a more controlled environmental condition if activity levels are primary environmental determinants of body composition. Comparison of these results with those from the literature, which presumably include both active and inactive families, should provide valuable new information regarding the roles of genes and gene-by-environment interactions for these measures.

The results for the adiposity measures of SF8 and %BF are consistent with the previous literature. As reviewed by Bouchard and Pérusse (5), previous studies suggested that a total of 35% of the variance for subcutaneous fat was due to

Table 4. Parameter estimates under the general and most parsimonious models

	SF8		%BF		FFM	
Parameter	General	Most parsimonious	General	Most parsimonious	General	Most parsimonious
fm	0.17 ± 0.11	0.18 ± 0.05	0.38 ± 0.09	0.37 ± 0.05	0.14 ± 0.11	[0]
fs	0.18 ± 0.09	[0.18]	0.35 ± 0.04	[0.37]	0.32 ± 0.08	0.23 ± 0.08
fd	0.04 ± 0.11	[0.18]	0.36 ± 0.08	[0.37]	0.16 ± 0.10	0.09 ± 0.08
ms	0.16 ± 0.10	[0.18]	0.35 ± 0.08	[0.37]	0.36 ± 0.08	0.39 ± 0.05
md	0.26 ± 0.09	[0.18]	0.40 ± 0.08	[0.37]	0.36 ± 0.09	[0.39]
ss	0.33 ± 0.14	[0.18]	0.41 ± 0.12	[0.37]	0.44 ± 0.11	[0.39]
dd	0.17 ± 0.12	[0.18]	0.43 ± 0.10	[0.37]	0.48 ± 0.09	[0.39]
sd	0.17 ± 0.10	[0.18]	0.37 ± 0.08	[0.37]	0.47 ± 0.07	[0.39]
Maximal heritability		34%*		62%*		65%†

*Maximal heritability ($[r_{sibling}+r_{parent\text{-}offspring}][1+r_{spouse}]/[1+r_{spouse}+2\ r_{spouse}\ r_{parent\text{-}offspring}]$) includes both genetic and familial environmental sources of variance and is adjusted for the degree of spouse resemblance.
†Maximal heritability is computed as twice the average familial correlation. However, assuming mitochondrial inheritance, maximal heritability is the average of mother-child and sibling correlations (39%).
Note: Parameters in square brackets were fixed at zero or were equated with a preceding paremeter.

familial factors. The estimate of 34% in the HERITAGE Family Study is remarkably similar. For %BF, previous studies suggested that 55% of the variance was due to familial factors (25% genetic and 30% environmental), which is consistent with the HERITAGE estimate of 62%. Also consistent with previous studies, significant spouse resemblance in the HERITAGE Family Study suggests that the source of the heritability is due at least in part to familial environmental factors. Therefore, for the adiposity measures, the sedentary nature of the HERITAGE families did not appear to affect the heritability estimates.

For FFM, however, the HERITAGE results are different. Previous studies (5) suggested that 40% of the variance was due to familial factors (30% to genes and 10% to environment). In HERITAGE, 65% of the variance could be accounted for by familial factors, which may be primarily (or largely) genetic in etiology given the nonsignificant spouse correlation, and with some irregularities associated with long-term intrauterine or maternally transmitted environmental effects. This much larger estimate than noted in the previous literature is consistent with the hypothesis that a sedentary lifestyle characterized by physical inactivity may be a factor that, when controlled for as in the HERITAGE, reduces the phenotypic variability, thus inflating the heritability.

An alternative explanation for the pattern of familial correlations for FFM includes the possibility of mitochondrial (as opposed to nuclear) genetic transmission, i.e., the correlations between sibling and mother-offspring pairs were equal (0.39) and were larger than the correlations between spouses and between fathers and their offspring (with sex-specific differences). Specifically, the spouse correlation was not significant, nor was the father-daughter correlation (0.09 ± 0.08), with the father-son correlation (0.23 ± 0.08) being moderate. The hypothesis of mitochondrial inheritance for FFM has some justification in the previous literature. Mitochondria are inherited primarily from the mother via cytoplasmic rather than nuclear sources, play a central role in the production of ATP at the cellular level, and have multiple copies of a circular DNA molecule (mtDNA) that undergoes replication. Multiple deletions of mtDNA are associated with abnormalities in muscle fibers and skeletal muscle (10). Interestingly, the multiple deletion disorder is also associated with an mtDNA interaction with an autosomal dominant nuclear gene. As reviewed by Smith and Alcivar (17), reciprocal cross-comparisons in pigs indicate a greater parent-offspring similarity with dam (female parent) than sire (male parent) for lean-to-fat ratio, as well as oxygen consumption and oxidative phosphorylation (the latter being influenced in part by enzymes encoded in the mtDNA). Similar patterns for oxygen consumption and lean mass are not surprising, given that the main tissue consuming O_2 in maximal exercise is muscle mass (~90%) (9) and that skeletal muscle mass accounts for more than 25% of the energy expended at rest.

In summary, the magnitude of familial resemblance for adiposity measures is consistent with results from the previous literature, suggesting that low to moderate levels of physical activity have little effect on familial aggregation. However, the results for FFM suggest several interesting

possibilities that need to be investigated further. If we assume a pattern of mitochondrial inheritance, then the magnitude of the familial effect is consistent with results from the previous literature. However, there is a residual father-child resemblance, raising the possibility of sex-specific interactions involving mtDNA and/or environmental factors, and perhaps even nuclear gene(s). Moreover, the etiological relationship between FFM and metabolic rate as assessed by oxygen consumption needs to be explored in more detail. These questions can be addressed using multilocus-multitrait segregation models (e.g. Ref. 3). Finally, if we assume a nonmitochondrial (or nuclear) genetic model, the familial effect on FFM increases considerably in these sedentary families as compared with those in previous studies, suggesting that a sedentary lifestyle reduces human variability in FFM and raises the genetic component.

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