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Major Gene Effect on Subcutaneous Fat Distribution in a Sedentary Population and Its Response to Exercise Training: The HERITAGE Family Study

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ABSTRACT Complex segregation analysis of baseline subcutaneous fat distribution and the change in response to exercise training (post-training minus baseline indices) was performed in a sample of 482 individuals from 99 Caucasian families who participated in the HERITAGE Family Study. The sum of skinfold (SF) thicknesses at eight sites, and the waist and hip circumferences were measured at baseline and after completing a 20-week exercise training program. The trunk-to-extremity ratio (TER) was calculated by dividing the sum of skinfold thicknesses at four trunk sites (subscapular + suprailiac + abdominal + midaxillary) by the sum of skinfold thicknesses at four extremity sites (triceps + biceps + medial calf + thigh). While SF was used to assess total subcutaneous adiposity, TER and the ratio of the waist-to-hip circumferences (WHR) were used to characterize subcutaneous fat distribution. Baseline TER and WHR were age-adjusted and age-SF-adjusted within four sex-by-generation groups. The changes of SF, TER, and WHR in response to training were adjusted for age effects alone and for the effects of age and baseline values. Baseline SF was influenced by a multifactorial component (30%) plus a major effect that may be environmental in origin accounting for 47% of the variance. Baseline TER was influenced by a multifactorial component (18%) and a major codominant gene ($q^2 = 0.10$), which accounted for 56% of the variance. The major gene effect was independent of total subcutaneous adiposity. Baseline WHR was regulated by a major codominant gene ($q^2 = 0.15$), which accounted for 48% of the variance. However, this major gene effect for baseline WHR should be interpreted with caution, given the estimates of the τ's under the general model. No familial effect was found for the changes in response to training for these subcutaneous adiposity and fat distribution phenotypes. Am. J. Hum. Biol. 12:600–609, 2000.

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It is recognized that abdominal obesity independent of the level of total body fat is associated with increased risk of cardiovascular diseases, noninsulin-dependent diabetes mellitus, and essential hypertension (Cann et al., 1994). Evidence of genetic influences on subcutaneous fat distribution has been reported (Pérusse et al., 1998; Bouchard et al., 1988; Selby et al., 1989, 1990; Donahue et al., 1992) along with support for environmental or lifestyle effects (Selby et al., 1990). The ratio of trunk-to-extremity (TER) skinfolds and the ratio of waist-to-hip (WHR) circumferences are frequently used to characterize subcutaneous fat distribution, while the sum of skinfold thicknesses (SF) is usually used to characterize general subcutaneous adiposity. Heritability estimates based on family studies are in the range of ~30–50% for subcutaneous fat distribution indices (Bouchard et al., 1991, 1993; Bouchard, 1997; Rice et al., 1999). Additionally, parent-offspring correlations are in the range of 0.18–0.27 in a cohort of children (Donahue et al., 1992), while mother–daughter and daughter–daughter correlations are 0.19–0.20 and 0.23–0.26, respectively, in a cohort of women (Sellers et al., 1994). Heritability estimates are 46% in adult male twins (Cardon et al., 1994), 36–61% among female twins (Rose et al., 1998), and 85% in early adolescent twins (Beunen et al., 1998). Further, findings from two studies support the view that the pattern of subcutaneous fat distribution is controlled by a Mendelian recessive major gene with a possible multifactorial effect (Hasstedt et al., 1989; Borecki et al., 1995a).

Regular vigorous physical exercise has consistently been associated with a favorable body fat distribution profile. It has been reported that the pattern of subcutaneous adiposity is not sensitive to energy expenditure and weight loss. However, a modest decrease in WHR in response to weight loss was observed in some studies (Cann et al., 1994). The current study presents results of complex segregation analyses of subcutaneous fat distribution phenotypes in response to a 20-week standardized endurance exercise training program.

Initial physical activity level was controlled by requiring that all participants were sedentary at baseline, i.e., not engaging in regular vigorous physical activity over the previous 6 months. In the present investigation, skinfold thicknesses at each of eight sites were measured and summed (SF) at baseline and after completing the 20-week supervised exercise program. Mean waist and hip circumferences were also measured before and after the training program. A major gene hypothesis for variation in subcutaneous fat distribution phenotypes at baseline and in response to exercise training is explicitly tested in the current study.

MATERIALS AND METHODS

Sample

The HERITAGE Family Study was designed to investigate the role of the genotype in cardiovascular, metabolic, and hormonal responses to aerobic exercise training and the contribution of regular exercise to changes in cardiovascular disease and diabetes risk factors. Details of the HERITAGE Family Study population and protocol are described in Bouchard et al. (1995).

A total of 482 individuals from 99 families (including one three-generation family which was then divided into two nuclear families) of Caucasian descent (233 males, 249 females) completed the training protocol. Participants with incomplete baseline or postexercise training measurements were excluded from the analysis for the response to training. A total of 479 individuals were eligible for the analysis for the response to training. Table 1 gives the sample sizes within each of four sex-by-generation groups (fathers, mothers, sons, and daughters) for baseline SF, TER, WHR, and the changes in response to training, respectively. Families of African American descent were also recruited and measured in the HERITAGE Family Study, but their results are not reported here. The study protocol was approved by the Institutional Review Board at each participating clinical center. Recruitment of families was based on extensive media publicity and advertisements at the four participating clinical centers.

The following entry criteria were applied to screen subjects for participation. First, individuals had to be between 17–65 years (17–40 years for children and ≤65 years for parents). Second, all participants were required to be sedentary at baseline. Third, a body mass index (BMI, weight (kg) / height $(m)^2$) <40 kg/m^2 was required unless a physician certified the subject was able to meet

TABLE 1. Means, SD, and SE for age, SF, TER, and WHR

Variables	No.	Means	SD (SE)	No.	Means	SD (SE)
	Fathers			Mothers		
Age, yrs	94	53.4[a]	5.5 (0.6)	91	52.1[a]	5.1 (0.5)
Baseline						
SF, mm	82	146.9[a,b]	49.7 (5.5)	78	196.4[a,b]	52.7 (6.0)
TER, mm/mn	82	1.89[a,b]	0.52 (0.06)	78	0.91[b]	0.21 (0.02)
WHR, cm/cm	94	0.96[a,b]	0.05 (0.01)	91	0.89[a,b]	0.07 (0.01)
Response to training						
SF, mm	80	−5.8	13.4 (1.49)	75	−7.0	17.4 (2.00)
TER, mm/mn	80	−0.03[b]	0.17 (0.02)	75	0.01[b]	0.11 (0.01)
WHR, cm/cm	93	−0.005	0.021 (0.002)	90	−0.006	0.026 (0.003)
	Sons			Daughters		
Age, yrs	139	25.4[a]	6.1 (0.5)	158	25.6[a]	6.5 (0.5)
Baseline						
SF, mm	132	122.8[a,b]	55.3 (4.8)	156	148.3[a,b]	50.8 (4.1)
TER, mm/mm	132	1.60[a,b]	0.47 (0.04)	156	0.90[b]	0.25 (0.02)
WHR, cm/cm	139	0.88[a,b]	0.07 (0.01)	158	0.81[a,b]	0.06 (0.01)
Response to training						
SF, mm	129	−7.8	14.3 (1.26)	153	−6.4	16.1 (1.30)
TER, mm/mm	129	−0.06[b]	0.19 (0.02)	153	−0.01[b]	0.10 (0.01)
WHR, cm/cm	139	−0.003	0.018 (0.001)	157	−0.005	0.029 (0.002)

[a]Significant ($P < 0.05$) mean differences for father–son or mother–daughter (within sex) comparisons.
[b]Significant ($P < 0.05$) mean differences for father–mother or son–daughter (within generation) comparisons.

the demands of the exercise tests and exercise training program. Fourth, resting blood pressure (BP) levels were ≤159 mm Hg for systolic BP and ≤99 mm Hg for diastolic BP in the absence of medications. Finally, participants were required to be in good general physical health in order to complete the 20-week exercise training program. Exclusion criteria are described in Bouchard et al. (1995).

Exercise training program

The training protocol is described in Skinner et al. (1999). Briefly, each individual trained on a cycle ergometer in the laboratory under supervision three times a week for 20 weeks. Participants exercised for 30 min at the heart rate associated with 55% of maximal oxygen intake during the first 2 weeks. The intensity or duration of exercise was adjusted every 2 weeks thereafter, so that participants were working for 50 min at the heart rate associated with 75% of baseline maximum oxygen intake during the last 6 weeks of training. The power output was adjusted automatically by a computer so that the desired training heart rate was maintained. All training sessions were supervised on site and adherence to the protocol was strictly monitored.

Measurements

SF at eight sites were measured with Harpenden calipers (Harrison et al., 1988) before and after the participants completed the 20-week standardized exercise training program. Each was based on the mean of two trials. A third trial was administered if the difference between the two measurements was greater than 1.0 mm, and the two closest measurements were averaged. When the third measurement fell equally between the first two, all three measurements were averaged. SF was the sum of skinfold thicknesses at eight sites. TER was calculated as the trunk sum (subscapular + suprailiac + abdominal + midaxillary) divided by the extremity sum (triceps + biceps + medial calf + thigh). WHR was calculated as the waist circumference divided by the hip circumference (Wilmore et al., 1997). The changes of variables in response to training were computed as the simple difference (post-training minus baseline).

Data adjustments

Baseline SF, TER, and WHR were adjusted for the effects of age within each of the four sex-by-generation groups on both the mean and variance (e.g., heteroscedasticity) using a stepwise multiple regression procedure (Rice et al. 1992). Briefly, 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 is independent of age, sex, and generation ef-

fects. Baseline TER was modestly correlated with baseline SF (from 0.23 in sons to 0.33 in daughters, except in fathers the correlation is nonsignificant), and baseline WHR was well correlated with baseline SF (from 0.40 in mothers to 0.81 in sons). In order to examine the hypothesis of genetic effects on fat distribution independent of overall subcutaneous adiposity, a similar set of stepwise regressions (by sex and generation groups) were also performed by regressing baseline TER (and WHR) on a polynomial in age and the linear baseline SF term (TER-f, WHR-f). The changes in response to training were similarly adjusted for the effects of polynomial in age, as well as the effects of polynomial in age and the respective baseline measures within each of the four sex by generation groups. The age-baseline-adjusted change in response to training indices the response to training independent of baseline levels. Each of the final adjusted phenotypes used in the genetic analysis was standardized to a mean of zero and an SD of one.

Segregation analysis

Segregation analysis, as implemented in the computer program POINTER (Lalouel et al., 1983; MacLean et al., 1976; Morton et al., 1983), was performed using the unified mixed model (Lalouel and Morton, 1981). This 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 with two alleles (A and a). The a allele is associated with higher trait values. Included in the model are seven parameters: the overall variance (V); the overall mean (u); the frequency of the a allele (q); the displacement 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, $\tau_1 = 1$, $\tau_2 = 0.5$ and $\tau_3 = 0$. When the three τ values are equal, no transmission of the major effect is obtained. The following three conditions are usually required in order to infer a major gene (Lalouel et al., 1983): 1) rejection of the no major effect hypothesis ($q = t = d = 0$); 2) nonrejection of the Mendelian transmission hypothesis (Mendelian τ's); and 3) rejection of the no transmission hypothesis (equal τ's). Hypothesis tests for nested models were carried out using the likelihood ratio test (LRT), which is the difference in minus twice the log-likelihood (-2 ln L) obtained under the two models. The likelihood ratio is approximately distributed as a χ^2, with the degrees of freedom being equal to the difference in the number of parameters estimated in the two models. In addition to the LRT, Akaike's Information Criterion (AIC), which is –2 ln L plus twice the number of estimated parameters, was used to compare nonnested models. The most parsimonious model is the one with the smallest AIC (Akaike, 1974).

RESULTS

The reproducibility of subcutaneous fat distribution measurements which were obtained on 3 days within a 3-week period was very high. Coefficients of variation for repeated measurements reached 4.5 to 11.6%, 1.0% and 0.7% for the eight skinfolds and the waist and hip circumferences, respectively. The intraclass correlations for repeated measurements were 0.96–0.99 for the eight skinfolds, and reached 0.99 for the waist and hip circumferences (Wilmore et al., 1997). Means and SD of baseline SF, TER, and WHR and the changes in response to training are given in Table 1. Based on a comparison of standard errors (SE), there were significant generation differences in mean baseline SF, TER, and WHR, with higher values in parents than in offspring within sex (except nonsignificant mother–daughter difference for mean baseline TER). There also were significant sex differences in mean baseline TER and WHR, with higher values in males than in females within generation, while baseline mean SF was significantly higher in females than in males within generation. Mean changes of SF, WHR, and TER (in sons only) decreased (significantly different from zero) in response to training. However, no significant generation and sex differences of the mean changes in response to training were observed, except for the mean TER change in

TABLE 2. Segregation analysis of baseline subcutaneous fat distribution

Models	df	−2 ln L	χ^2	*P*	AIC	−2 ln L	χ^2	*P*	AIC
			SF				TER-f[a]		
1. General Mendelian	0	788.37	—	—	802.37	772.14	—	—	786.14
2. No multifactorial (H = Z = 0)	2	795.35	6.98	0.031	805.35	782.57	10.43	0.005	792.57
3. No major effect (d = t = q = 0)	3	812.79	24.42	<0.001	820.79	827.50	55.36	<0.001	835.50
4. No familial (d = t = q = H = Z = 0)	5	827.77	39.40	<0.001	831.77	872.14	100.00	<0.001	876.14
5. No generation difference (Z = 1)	1	788.45	0.08	0.777	800.45	772.35	0.21	0.647	784.35
6. Recessive (d = 0)	1	788.37	0.00	1.000	800.37	776.87	4.73	0.030	788.87
7. Additive (d = 0.5)	1	799.65	11.28	<0.001	811.65	798.02	25.88	<0.001	810.02
8. Dominant (d = 1)	1	800.03	11.66	<0.001	812.03	799.15	27.01	<0.001	811.15
9. Free τ's (d = 0)	3	777.09	11.28	0.010	795.09				
Free τ's	3					770.03	2.11	0.550	790.03
10. Equal τ's (1-q; d = 0)	3	777.22	0.13	0.988	789.22				
Equal τ's	3					778.26	8.23	0.041	792.26
			WHR				WHR-f		
1. General Mendelian	0	794.05	—	—	808.05	782.42	—	—	796.42
2. No multifactorial (H = Z = 0)	2	794.17	0.12	0.942	804.17	782.97	0.55	0.760	792.97
3. No major effect (d = t = q = 0)	3	809.93	15.88	0.001	817.93	784.40	1.98	0.577	792.40
4. No familial (d = t = q = H = Z = 0)	5	851.24	57.19	<0.001	855.24	836.98	54.56	<0.001	840.98
5. No gen. diff. (d = t = q = 0, Z = 1)	4					786.24	3.82	0.431	792.24
6. Recessive (d = 0, H = Z = 0)	3	799.01	4.96	0.175	807.01	797.01	14.59	0.002	805.01
7. Additive (d = 0.5, H = Z = 0)	3	801.10	7.05	0.070	809.10	785.93	3.51	0.319	793.93
8. Dominant (d = 1, H = Z = 0)	3	801.47	7.42	0.060	809.47	795.29	12.87	0.005	803.29
9. Free τ's (H = Z = 0)	3	789.80	4.37	0.224	805.80				
Free τ's (d = 0.5, H = Z = 0)	3					784.76	1.17	0.760	798.76
10. Equal τ's (1-q; H = Z = 0)	3	822.94	33.14	<0.001	832.94				
Equal τ's (1-q; d = 0.5, H = Z = 0)	3					836.13	51.37	<0.001	844.13

[a]The results for age-adjusted TER and age-SF-adjusted TER (TER-f) were similar; only the results for the age-SF-adjusted TER are presented here.

response to training with small but significant sex differences within generation.

Significant age and SF terms with percentages of variance accounted for in each of the sex-by-generation groups were as follows. For baseline SF, age accounted for 21.3% (age) and 4.1% (age^3) of the variance in sons and daughters, respectively. For age-adjusted baseline TER, age accounted for 13.3% (age) of the variance in sons. For age-SF-adjusted baseline TER, the covariates accounted for 7.3% (SF), 13.3% (age) and 15.2% (SF, age^3) of the variance in mothers, sons, and daughters, respectively. For age-adjusted baseline WHR, age accounted for 5.1%, 28.2%, and 2.9% of the variance in fathers, sons, and daughters, respectively. For age-SF-adjusted baseline WHR, the covariates accounted for 35.9% (SF, age), 16.1% (SF), 69.4% (SF, age), and 29.5% (SF) of the variance in fathers, mothers, sons, and daughters, respectively. For age-adjusted response to training, age was not a significant predictor of TER and WHR changes in response to training. However, age accounted for 4.5% (age^2) of the variance in sons for age-adjusted SF change in response to training, but was not significant in any other group. For age-baseline-adjusted change in response to training, baseline terms were not significant in parents, but were in offspring. Baseline values accounted for 8.8% in sons and 4.7% in daughters for SF change in response to training, 10.6% in sons and 11.1% in daughters (baseline, age^2, age^3) for TER change in response to training, and 10.5% in daughters for WHR change in response to training, respectively. Baseline SF was not a significant predictor of TER or WHR change in response to training.

Segregation analysis results are summarized in Table 2 for baseline SF, TER-f, WHR, and WHR-f. The results for age-adjusted TER and age-SF-adjusted TER (TER-f) were similar. Only the results for the age-SF-adjusted TER are presented in Table 2. The parameter estimates under the most parsimonious segregation models are given in Table 3. For age-adjusted baseline SF (Table 2), each of the hypotheses of no multifactorial effect (model 2; $\chi^2_2 = 6.98$, $P = 0.03$), no major effect (model 3; $\chi^2_3 = 24.42$, $P < 0.01$), and no familial effect (model 4; $\chi^2_5 = 39.40$, $P < 0.01$) was rejected. This suggested the presence of a multifactorial component as well as a major effect. Further, the hypothesis of no generation difference in the multifactorial component was not rejected (model 5; $\chi^2_1 = 0.08$,

TABLE 3. Parsimonious segregation models for baseline subcutaneous fat distribution

Variables	d	t	q	H	Z	ME (%)[a]
SF[b]	[0]	1.90 ± 0.10	0.40 ± 0.03	0.30 ± 0.08	0.39 ± 0.23	47% ± 6%
TER[c]	0.17 ± 0.05	2.90 ± 0.19	0.32 ± 0.03	0.17 ± 0.05	[1]	54% ± 11%
TER-f[d]	0.16 ± 0.05	3.01 ± 0.19	0.31 ± 0.03	0.18 ± 0.05	[1]	56% ± 11%
WHR[e]	0.25 ± 0.06	2.14 ± 0.15	0.39 ± 0.05	[0]	[0]	48% ± 8%
WHR-f	[0]	[0]	[0]	0.50 ± 0.06	[1]	—

[a]Percentages accounted for by major effects.
[b]Under the general model, $\tau_1 = 0.61 \pm 0.05$, $\tau_2 = 0.60 \pm 0.51$, $\tau_3 = 0.72 \pm 0.21$; and under the equal τ's model, $\tau_1 = \tau_2 = \tau_3 = 0.60 \pm 0.00$.
[c]Under the general model, $\tau_1 = 1.00 \pm 0.00$, $\tau_2 = 0.74 \pm 0.05$, $\tau_3 = 0.00 \pm 0.00$.
[d]Under the general model, $\tau_1 = 1.00 \pm 0.00$, $\tau_2 = 0.68 \pm 0.06$, $\tau_3 = 0.00 \pm 0.00$.
[e]Under the general model, $\tau_1 = 1.00 \pm 0.00$, $\tau_2 = 0.31 \pm 0.06$, $\tau_3 = 0.74 \pm 0.13$.

$P = 0.78$). Both the additive (model 7; $\chi^2_1 = 11.28$, $P < 0.01$) and dominant (model 8; $\chi^2_1 = 11.66$, $P < 0.01$) hypotheses were rejected, whereas a recessive (model 6; $\chi^2_1 = 0.00$, $P = 1.00$) mode of inheritance fit the data. Tests on transmission probabilities were performed under the parsimonious Mendelian hypothesis (model 6, a major recessive gene and a multifactorial component). While Mendelian τ's were rejected (model 6 – model 9: $\chi^2_3 = 11.28$, $P = 0.01$), the constrained equal τ's ($t_1 = t_2 = t_3 = 1–q$) hypothesis was not rejected (model 9 – model 10: $\chi^2_3 = 0.13$, $P = 0.99$). According to the likelihood ratio and the AIC, the hypothesis of non-Mendelian transmission (equal τ's) "best" fit the data. The major effect appeared to be environmental in nature, and it accounted for 47% of the variance with a noticeable multifactorial component (accounting for 30% of the variance).

Segregation analysis was performed on both the age-adjusted baseline TER and age-SF-adjusted TER separately. As similar results were obtained, only those for the age-SF-adjusted TER are given in Table 2. All three hypotheses (models 2–4) of no multifactorial, no major, and no familial effects were rejected, which suggests the presence of a multifactorial component and a major effect. The hypothesis of no generation difference in the multifactorial component was not rejected (model 5). The recessive, additive, and dominant hypotheses were all rejected (models 6–8). Tests on transmission probabilities were performed under the parsimonious hypothesis (model 1, a general Mendelian model). While constrained equal τ's hypothesis was rejected (model 10, model 9: $\chi^2_3 = 8.23$, $P = 0.041$), Mendelian τ's hypothesis was not rejected (model 1–9: $\chi^2_3 = 2.11$, $P = 0.550$). According to the likelihood and the AIC, the hypothesis of no generation difference in the multifactorial component and Mendelian τ's (model 5) was the most parsimonious. The major codominant locus accounted for 56% of the variance, with a noticeable multifactorial component (18%) (Table 3).

For age-adjusted baseline WHR, there was a major effect (models 3 and 4) but no multifactorial effect (model 2). Therefore, the major effect parameters were tested with H = Z = 0. The modes of inheritance were not differentiable (models 6–8). Therefore, tests on transmission probability were performed with *d* unrestrained. While the constrained equal τ's hypothesis was rejected (model 10, model 9: $\chi^2_3 = 33.14$, $P < 0.01$), Mendelian τ's were not rejected (model 2–9: $\chi^2_3 = 4.37$, $P = 0.22$). These results provided consistent evidence to infer a Mendelian codominant gene regulating baseline WHR. According to the likelihood ratio and the AIC, the hypothesis of no multifactorial component provided the "best" fit (model 2). The major gene effect accounted for 48% of the variance, with the allele frequency leading to high values of baseline WHR being 0.39.

Segregation analysis also was performed on the age-SF-adjusted baseline WHR. Although there was a familial effect (model 4), it was not differentiable between a multifactorial component (model 2) and a major effect (model 3). In the absence of a major effect, there was no generation difference in the multifactorial component (model 5). In the absence of a multifactorial component, the hypotheses of recessive and dominant modes of inheritance were rejected (models 6 and 8), but that of an additive mode fit the data (model 7). Tests on transmission probabilities were performed under the model with a major additive gene and no multifactorial component (model 7). The Mendelian τ's hypothesis (model 9) was not rejected, while the equal τ's hypothesis (model 10)

was rejected. However, according to the likelihood and the AIC, the hypothesis of no generation differences in the multifactorial component in the absence of a major effect (model 5) provided the "best" fit. The heritability in parents and offspring was about 50%.

Although segregation analysis was performed on changes in SF, TER, and WHR in response to training (age-adjusted as well as age-baseline-adjusted), no familial effect was significant (model 4 nonsignificant), and the results are thus not presented.

DISCUSSION

This investigation was designed to examine the hypotheses of major gene effects for baseline SF, TER, and WHR in sedentary Caucasian families as well as for the responses to a 20-week endurance exercise training program. As physical activity level was controlled at baseline, it is interesting to compare our findings from these physically inactive families with those from other heterogeneous samples, which presumably included a mixture of active and inactive families. Moreover, this is the first study to assess a major gene hypothesis for baseline WHR, and for changes in SF, TER, and WHR in response to regular exercise training.

Baseline SF indicates overall subcutaneous adiposity. Both a major effect and a multifactorial effect were found influencing baseline SF (Table 2, models 2–4 were rejected). Further, there was a generation difference in the multifactorial effect (model 5 was rejected), and the major effect appeared to be recessive inheritance (model 6 was not rejected while models 7 and 8 were rejected). In order to safeguard against false inference of a major gene in segregation analysis (Lalouel et al., 1983), it has become common to require nonrejection of the Mendelian-transmission hypothesis (model 9, free τ's or most general model) and rejection of the nontransmitted hypothesis (model 10, equal τ's or environmental model). In this study, model 9 was rejected, whereas model 10 was not rejected, which suggested that the transmission from parents to offspring was ambiguous, i.e., Mendelian or environmental (nontransmitted) in origin. As the AIC suggested that the most parsimonious model was model 10, the transmission from parents to offspring appeared to be environmental in origin, and evidence to infer a major recessive gene for baseline SF was not adequately convincing. In a simulation study, rates of Mendelian inference varied from 22–50% under recessive inheritance (Borecki et al., 1995b). Segregation analysis can also be sensitive to ascertainment bias with limited ability to distinguish among the many possible modes of inheritance and the number of distinct genes influencing a complex trait (Lander and Schork, 1994). In this study, we can conclude that baseline SF was influenced by a major effect, which accounted for 47% of the variance but the effect appeared to be familial environmental in origin. An additional multifactorial component in this study (heritability of 30% in offspring) for baseline SF levels is consistent with other data from the HERITAGE families (34%) using a familial correlation methodology (Rice et al., 1997).

Baseline TER was influenced by a major codominant gene as well as multifactorial effects (heritability of 18%). The putative major gene accounted for 56% of the variance, and an estimated 10% (q^2) of the sample had the homozygous *aa* genotype leading to high values of baseline TER (i.e., increased trunk as compared to extremity fat deposition). The fact that similar results were found in age-adjusted and age-SF-adjusted baseline TER suggests that baseline TER was relatively independent of baseline SF, i.e., primarily unaffected by the level of subcutaneous adiposity. Only two segregation analyses of subcutaneous fat distribution (TER) have been previously performed (Bouchard, 1997). Findings from the current study are consistent with Borecki et al. (1995a), who found that TER (age-sex-generation-total fat mass-adjusted vs. age-sex-generation-SF-adjusted in the current study) was under the influence of a major locus (recessive gene frequency of 0.35 vs. codominant gene frequency of 0.31 in the current study) which accounted for 37% (vs. 56% in the current study) of the variance with a multifactorial component (29% of heritability vs. 18% in the current study). The other study (Hasstedt et al., 1989) defined a relative-fat-distribution index (RFPI) as the ratio of subscapular skinfold thickness to the sum of subscapular and suprailiac skinfold thicknesses (age-sex-generation-adjusted). A major recessive gene influencing RFPI was supported, which accounted for 42% (vs. 56% in the current study) of the variance with an addi-

tional 10% (vs. 18% in the current study) of the variance accounted for by a multifactorial component.

WHR is frequently used in clinical and epidemiological studies to characterize or estimate overall body fat distribution (Caan et al., 1994). In the present study, baseline WHR may be influenced by a putative major codominant gene which accounted for 48% of the variance, and an estimated 15% (q^2) of the sample may carry the homozygous *aa* genotype leading to high values of baseline WHR. It is of interest that when baseline WHR was adjusted for the effect of total SF, the major effect disappeared and, instead, a multifactorial component (heritability of 50%) emerged. However, the transmission probabilities do not look Mendelian under the free τ's model (see footnote to Table 3). Thus, while these results statistically support a major gene effect, the general pattern is less convincing than that for TER. It is possible that the major gene previously detected for total fat (Rice et al., 1993; Comuzzie et al., 1995) may also impact on the WHR, given the fact that the support for a major locus disappears after adjusting for total subcutaneous adiposity.

In response to the 20-week exercise training program, the mean change in SF (significantly different from zero) ranged from –0.58 in fathers to –0.78 cm in sons, but the mean changes in TER (significantly different from zero in sons only) and WHR (significantly different from zero) were also quite modest (Table 1). Theoretically, just because the overall mean changes in response to training are close to zero, we cannot conclude that there is no familiality, because the changes in response to training may cluster in families. The presence of a familial effect influencing subcutaneous fat distribution phenotypes in response to exercise training was explore, but there was no evidence for familiality or major gene action. Previously, a series of studies were performed in male monozygotic (MZ) twin pairs to investigate the role of the genotype in determining the response to changes in positive energy balance induced by short-term (Poehlman et al., 1986a) and long-term overfeeding (Bouchard et al., 1990), or in negative energy balance induced by short-term (Poehlman et al., 1986b) and long-term exercise training (Bouchard et al., 1994). Changes in body fat in response to short-term (Poehlman et al., 1986a; Bouchard et al., 1988; Poehlman and Horton, 1989) or long-term overfeeding (Bouchard et al., 1990) to a large extent have a genetic basis with undetermined genetic characteristics. Although genotype is closely associated with changes in fat free mass, heredity is not a major factor influencing changes in body fat and adipose tissue indicators in response to short-term exercise training (Poehlman et al., 1986b, 1987; Poehlman and Horton, 1989). In contrast, a study of seven male identical twin pairs suggests that the genotype may play a significant role in determining the changes of subcutaneous fat in response to long-term exercise training, i.e., biological adaptability (Bouchard et al., 1994; Bouchard and Tremblay, 1997). Further studies are justified to explore the genetic differences in metabolic pathways, which may potentially induce interesting variations of subcutaneous fat distribution in energy expenditure.

Subcutaneous fat distribution indices and the changes in responses to training are complex phenotypes. In addition to genetic effects, lifestyle and behavioral influences as well as possible underlying interactions may also contribute to individual differences (Selby et al., 1990). In summary, baseline subcutaneous adiposity was influenced by both a multifactorial effect and a major effect, which may be familial environmental in origin. Both baseline TER and WHR may be influenced by putative major codominant loci with additional multifactorial factors for TER. However, the results for baseline WHR should be interpreted with caution, given the lack of support for a Mendelian pattern of transmission under the general model. Finally, there was no evidence to support a familial hypothesis for the responsiveness of these subcutaneous fat distribution phenotypes to exercise training.

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LITERATURE CITED

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

Beunen G, Maes HH, Vlietinck R, Malina RM, Thomis M, Feys E, Loos R, Derom C. 1998. Univariate and multivariate genetic analysis of subcutaneous fatness and fat distribution in early adolescence. Behav Genet 28:279–288.

Borecki IB, Rice T, Pérusse L, Bouchard C, Rao DC. 1995a. Major gene influence on the propensity to store fat in trunk versus extremity depots: evidence from the Québec family study. Obes Res 3:1–8.

Borecki IB, Higgins M, Schreiner PJ, Arnett DK, Mayer DE, Hunt SC, Province MA. 1998. Evidence for multiple determinants of the body mass index: the National Heart, Lung, and Blood Institute family heart study. Obes Res 6:107–114.

Bouchard C. 1990. Variation in human body fat: the contribution of the genotype. In: Bray GA, Ricquier D, Spiegelman BM, editors. Obesity: towards a molecular approach. New York: Alan R. Liss. p 17–28.

Bouchard C. 1997. Genetic determinants of regional fat distribution. Hum Reprod 12(Suppl 1):1–5.

Bouchard C, Tremblay A. 1997. Genetic influences on the response of body fat and fat distribution to positive and negative energy balances in human identical twins. J Nutr 127:943S–947S.

Bouchard C, Tremblay A, Després JP, Poelman ET, Thériault G, Nadeau A, Lupien P, Moorjani S, Dussault J. 1988. Sensitivity to overfeeding: the Quebec experiment with identical twins. Prog Food Nutr Sci 12:45–72.

Bouchard C, Tremblay A, Després J-P, Nadeau A, Lupien PJ, Thériault G, Dussault J, Moorjani S, Pinault S, Fournier G. 1990. The response to long-term overfeeding in identical twins. N Engl J Med 322:1477–1482.

Bouchard C, Després J-P, Mauriège P, Marcotte M, Chagnon M, Dionne FT, Bélanger A. 1991. The genes in the constellation of determinants of regional fat distribution. Int J Obes 15:9–18.

Bouchard C, Després JP, Mauriège P. 1993. Genetic and nongenetic determinants of regional fat distribution. Endocr Rev 14:72–93.

Bouchard C, Tremblay A, Després J-P, Thériault G, Nadeau A, Lupien PJ, Moorjani S, Prud'homme D, Fournier G. 1994. The response to exercise with constant energy intake in identical twins. Obes Res 2: 400–410.

Bouchard C, Leon AS, Rao DC, Skinner JS, Wilmore JH, Gagnon J. 1995. The HERITAGE family study: aims, design and measurement protocol. Med Sci Sports Exerc 27:721–729.

Cann B, Armstrong MA, Selby JV, Sadler M, Folsom AR, Jacobs D, Slattery ML, Hilner JE, Roseman J. 1994. Changes in measurements of body fat distribution accompanying weight change. Int J Obes 18:397–404.

Cardon LR, Carmelli D, Fabsitz RR, Reed T. 1994. Genetic and environmental correlations between obesity and body fat distribution in adult male twins. Hum Biol 66:465–479.

Comuzzie AG, Balangero J, Mahaney MC, Mitchell BD, Hixson JE, Samollow PB, Stern MP, MacCluer JW. 1995. Major gene with sex-specific effects influences fat mass in Mexican Americans. Genet Epidemiol 12: 475–488.

Donahue RP, Prineas RJ, Gomez O, Hong CP. 1992. Familial resemblance of body fat distribution: the Minneapolis children's blood pressure study. Int J Obes 16:161–167.

Harrison GG, Buskirk ER, Lindsay-Carter JE. 1988. Skinfold thicknesses and measurement techniques. In: Lohman TG, Roche AF, editors. Anthropometric standardization reference manual. Champaign, IL: Human Kinetics. p 55–80.

Hasstedt SJ, Ramirez ME, Kuida H, Williams RR. 1989. Recessive inheritance of a relative fat pattern. Am J Hum Genet 45:917–925.

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.

Lander ES, Schork NJ. 1994. Genetic dissection of complex traits. Science 265:2037–2048.

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

Morton NE, Rao DC, Lalouel JM. 1983. Methods in genetic epidemiology. New York: Karger.

Pérusse L, Leblanc C, Bouchard C. 1988. Intergeneration transmission of physical fitness in the Canadian population. Canadian Journal of Sport Sciences 13:8–14.

Poehlman ET, Horton ES. 1989. The impact of food intake and exercise on energy expenditure. Nutr Rev 47:129–137.

Poehlman ET, Tremblay A, Després JP, Fontaine E, Pérusse L, Thériault G, Bouchard C. 1986a. Genotype-controlled changes in body composition and fat morphology following overfeeding in twins. Am J Clin Nutr 43:723–731.

Poehlman ET, Tremblay A, Nadeau A, Dusseault J, Thériault G, Boucgard C. 1986b. Heredity and changes in hormones and metabolic rates with short-term training. Am J Physiol 250:E711–777.

Poehlman ET, Tremblay A, Marcotte M, Pérusse L, Thériault G, Bouchard C. 1987. Heredity and changes in body composition and adipose tissue metabolism after short-term exercise-training. Eur J Appl Physiol 56:398–402.

Rice T, Borecki IB, Bouchard C, Rao DC. 1992. Commingling analysis of regional fat distribution measures: the Québec family study. Int J Obes Relat Metab Disord 16:831–844.

Rice T, Borecki IB, Bouchard C, Rao DC. 1993. Segregation analysis of fat mass and other body composition measures derived from underwater weighing. Am J Hum Genet 52:967–973.

Rice T, Daw EW, Gagnon J, Bouchard C, Leon AS, Skinner JS, Wilmore JH, Rao DC. 1997. Familial resemblance for body composition measures: the HERITAGE family study. Obes Res 5:557–562.

Rice T, Pérusse L, Bouchard B, Rao DC. 1999. Familial aggregation of body mass index and subcutaneous fat measures in the longitudinal Québec family study. Genet Epidemiol 16:316–334.

Rose KM, Newman B, Mayer-Davis EJ, Selby JV. 1998. Genetic and behavioral determinants of waist-hip ratio and waist circumference in women twins. Obes Res 6:383–392.

Selby JV, Newman B, Quesenberry CP, Fabsitz RR, King M-C, Meaney FJ. 1989. Evidence of genetic in-

fluence on central body fat in middle-age twins. Hum Biol 61:179–193.
Selby JV, Newman B, Quesenberry CP, Fabsitz RR, Carmelli D, Meaney FJ, Slemenda C. 1990. Genetic and behavioral influences on body fat distribution. Int J Obes 14:593–602.
Sellers TA, Drinkard C, Rich SS, Potter JD, Jeffery RW, Hong CP, Folsom AR. 1994. Familial aggregation and heritability of waist-to-hip ratio in adult women: the Iowa Women's Health study. Int J Obes 18:607–613.
Skinner JS, Wilmore KM, Krasnoff JB, Jaskólski A, Jaskólska A, Gagnon J, Province MA, Leon AS, Rao DC, Wilmore JH, Bouchard C. 1999. Adaptation to a standardized training program and changes in fitness in a large, heterogeneous population: the HERITAGE family study. Med Sci Sports Exerc (in press).
Wilmore JH, Stanforth PR, Domenick MA, Gagnon J, Daw EW, Leon AS, Rao DC, Skinner JS, Bouchard C. 1997. Reproducibility of anthropometric and body composition measurements: the HERITAGE family study. Int J Obes 21:297–303.