A Genetic Study of Sex Hormone–Binding Globulin Measured Before and After a 20-Week Endurance Exercise Training Program: The HERITAGE Family Study

Ping An, Treva Rice, Jacques Gagnon, Yuling Hong, Arthur S. Leon, James S. Skinner, Jack H. Wilmore, Claude Bouchard, and D.C. Rao

Familial aggregation and a major gene effect were assessed for baseline serum sex hormone–binding globulin (SHBG) levels and the response (post-training minus baseline) to a 20-week endurance training program in a selected sample of 428 non-obese nonhypertensive individuals from 99 white families who were sedentary at baseline in the HERITAGE Family Study. Baseline SHBG levels were not normally distributed, and were therefore logarithmically transformed prior to genetic analyses. In a sample without postmenopausal mothers, maximal (genetic and familial environmental) heritabilities were 50% averaged across sexes, 73% in men, 50% in women, and 31% in men versus women for the age-body mass index (BMI)–adjusted baseline. The estimate reached 64% when the baseline was further adjusted for the effects of estradiol, fasting insulin, and testosterone levels. For the response to training, no sex difference was found and the heritability reached about 25% to 32%. Segregation analysis was separately performed in the whole sample and in the sample without postmenopausal mothers. In addition to a multifactorial effect for both the baseline and the response to training, a major effect for the baseline appeared to be familial environmental in origin, whereas a major effect for the response to training was Mendelian in nature. The major gene effect for the response to training in the whole sample was undetectable in the sample without postmenopausal mothers, and it is therefore possible that the postmenopausal mothers, characterized by decreased sex hormones with or without estrogen replacement therapy for menopause, produced some confounding effects. In addition, the reduced sample size might also be a plausible candidate explanation. The novel finding in this study is that baseline SHBG levels and the response to training were influenced by a multifactorial effect with sex difference for the baseline. The response to training appeared to be additionally influenced by a single recessive locus that is independent of baseline SHBG levels.

HUMAN SEX HORMONE–BINDING globulin (SHBG) is a circulating steroid-binding plasma glycoprotein synthesized by hepatocytes that not only specifically binds and transports androgens and estradiol but also regulates the bioavailability and metabolic clearance of sex steroids.[1-2] Recent studies have identified a specific membrane receptor for SHBG (SHBG-R). More interestingly, the SHBG/SHBG-R complex was found to be an amplifier of androgen action in prostate cells and an antagonist of estradiol action in breast cancer cells mediated via cyclic 3′,5′-adenosine monophosphate and successive activation/deactivation of the intracellular receptor, protein kinase A.[3-4] Increased levels of SHBG are associated with cirrhosis of the liver and anorexia nervosa, while decreased levels of SHBG have been associated with polycystic ovarian syndrome and hirsutism. Low levels of SHBG are also associated with increased triglycerides, decreased high-density lipoprotein cholesterol, obesity, and other cardiovascular risk factors.[5-10]

The genetic heritability for SHBG levels in twin studies is negligible (≤5%).[11-13] However, a significant heritability (62%) was reported in a recent twin study[14] in which SHBG levels were measured using a radioimmunometric procedure rather than a competitive protein binding technique.[15-16] Furthermore, in the San Antonio Family Heart Study, the heritability for SHBG measured using a radioimmunometric procedure (Diagnostic System Laboratories, Webster, TX) was estimated to be 31%.[17] Results of segregation analysis for SHBG levels were not reported previously. According to Bérubé et al,[18] the SHBG structural gene is located on human chromosome 17p12-13; however, the effects of this locus remain unknown, and other unidentified loci may influence the variation of SHBG levels in individuals.[17]

Conflicting results were found in previous reports on the acute SHBG response to exercise.[19-22] While Tegelman et al[20] found no change in SHBG levels in response to exercise, Häkkinen et al[19] and Caballero et al[21] found an increase and a decrease in SHBG levels in response to training, respectively. It is interesting to note that when the same exercise protocol was administered in 2 different experiments on long distance runners, Bonifazi and Lupo[22] found that SHBG levels were decreased 1 hour after exercise in the first experiment but increased at the end of running in the second experiment. Although the exact cause is uncertain, serum SHBG levels increased (and insulin levels decreased) in response to a 21-day low-fat, high–complex-carbohydrate, and high-fiber diet with regular aerobic exercise intervention.[23] The metabolic clearance rate and half-life of SHBG should also be taken into account for comments on the SHBG response to exercise training. No studies have previously explored a familial basis for changes in SHBG levels in response to endurance exercise training.

From the Division of Biostatistics and Departments of Genetics and Psychiatry, Washington University School of Medicine, St Louis, MO; Physical Activity Sciences Laboratory, Laval University, Quebec, Canada; School of Kinesiology and Leisure Studies, University of Minnesota, Minneapolis, MN; Department of Kinesiology, Indiana University, Bloomington, IN; Department of Health and Kinesiology, Texas A&M University, College Station, TX; and Pennington Biomedical Research Center, Louisiana State University, Baton Rouge, LA.

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Address reprint requests to Ping An, MD, Division of Biostatistics, Campus Box 8067, Washington University School of Medicine, 660 S Euclid Ave, St Louis, MO 63110-1093.

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The initial physical activity level was controlled for in the HERITAGE Family Study by requiring all participants to be sedentary at baseline, ie, not engaging in regular physical activity over the previous 6 months. This study is unique in that SHBG levels were assessed before and after a 20-week endurance exercise training program in intact families, so the familial aggregation and a major gene hypothesis for both baseline SHBG and the response to training data can be assessed. It is known that estradiol levels are positively associated with SHBG levels, whereas obesity, insulin, and testosterone levels are negatively associated with SHBG levels.[24-26] Our data were accordingly adjusted for the effects of these variables to allow precise assessment of the effects of genetic influences and familial environmental impacts. Moreover, postmenopausal mothers, with their sex hormone levels decreased significantly, may have received hormone (estrogen) replacement therapy for menopause in this study, which complicates the data interpretation. Familial aggregation and segregation analyses were therefore performed in a sample without the postmenopausal mothers. Since the sample size is more sensitive to segregation analysis, the major gene hypothesis was additionally and separately assessed in the whole sample in the present study.

SUBJECTS 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. A description of the HERITAGE Family Study protocol, population, and inclusion and exclusion criteria has been published.[27]

A total of 428 individuals (not including postmenopausal mothers) from 99 white families (229 men and 199 women) were available for this study. Participants with incomplete pre- and post-training SHBG measurements were excluded from the sample. Of 90 mothers in the whole sample, 44 were not premenopausal. Table 1 shows the sample size within 4 sex × generation groups (fathers, premenopausal mothers, sons, and daughters) for baseline SHBG levels and the response to training. Black families also were recruited and measured in the HERITAGE Family Study, but the results are not included in this report.

Exercise Training Program

Following the initial test battery, subjects completed a 20-week endurance training program (3 days per week for a total of 60 exercise sessions) on cycle ergometers (Universal Aerobicycle, Cedar Rapids, IA) that were computer-controlled to maintain the participants' heart rate at a level associated with a fixed percentage of their maximal oxygen consumption ($\dot{V}O_2$max). The training program started at 55% $\dot{V}O_2$max for 30 minutes per session and gradually increased to 75% $\dot{V}O_2$max for 50 minutes per session during the last 6 weeks of training. The full test battery was administered again at the conclusion of the training program. (See Skinner et al[28] for details concerning the training program.) All training sessions were supervised on-site, and adherence to the protocol was strictly monitored.

Measurements

Blood samples were collected from an antecubital vein into vacutainer tubes without anticoagulant in the morning after a 12-hour fast, with the participants in a semirecumbent position. They were obtained twice at baseline (at least 24 hours apart) and twice following the training program (24 hours after the exercise training session). For eumenorrheic women, all samples were obtained in the early follicular phase of the menstrual cycle. Fasting serum was prepared according to a standard protocol. After centrifugation of the blood at 2,000 × *g* for 15 minutes at 4°C, 2 aliquots of 2 mL in cryogenic tubes were frozen at −80°C until shipment in the following month. Serum samples from the 3 US HERITAGE Clinical Centers were shipped in the frozen state to the HERITAGE Steroid Core Laboratory at the Molecular Endocrinology Laboratory of Laval University Medical Center for analysis. Serum SHBG quantitative measurements were determined with a IRMA-count immunoradiometric assay using iodine 125 (Diagnostic System Laboratories).

The reproducibility of the baseline SHBG level was very high in the present study. Technical errors for repeated measures were 4.1 nmol/L in 325 men and 11.7 nmol/L in 420 women. Intraclass correlations for repeated measures were greater than .97 in men and women. The coefficient of variation for repeated measures was 11% and 15% in men and women, respectively. Thus, the phenotypes were measured with good precision, which is necessary for a meaningful interpretation of the response to training.

Table 1. Unadjusted Baseline SHBG and the Change in Response to Training

Variable	Fathers No.	Fathers Mean ± SD	Mothers‡ No.	Mothers‡ Mean ± SD
Age (yr)	93	53.5 ± 5.4*†	46	48.6 ± 2.6†
Baseline				
Weight (kg)	93	87.5 ± 15.3*	46	70.8 ± 12.9*†
BMI (kg/m²)	93	28.3 ± 4.5†	46	27.0 ± 5.1†
SHBG (nmol/L)	93	44.4 ± 17.6*†	46	83.8 ± 45.3*
Log (SHBG)	93	3.7 ± 0.4*†	46	4.3 ± 0.6*
Response to training				
Weight (kg)	93	−0.4 ± 1.8†	46	−0.4 ± 1.9
BMI (kg/m²)	93	−0.1 ± 0.6	46	−0.1 ± 0.8
SHBG (nmol/L)	93	−0.1 ± 8.3*	46	−7.9 ± 25.3*†
	Sons		Daughters	
Age (yr)	136	25.4 ± 6.2†	153	25.5 ± 6.4†
Baseline				
Weight (kg)	136	82.5 ± 16.9*	153	63.8 ± 13.0*†
BMI (kg/m²)	136	25.7 ± 4.9*†	153	23.5 ± 4.3*†
SHBG (nmol/L)	136	35.1 ± 15.0*†	153	87.6 ± 47.4*
Log (SHBG)	136	3.5 ± 0.4*†	153	4.3 ± 0.5*
Response to training				
Weight (kg)	136	−0.3 ± 2.3†	153	0.0 ± 2.2
BMI (kg/m²)	136	−0.1 ± 0.7	153	0.0 ± 0.8
SHBG (nmol/L)	136	0.1 ± 8.0	153	3.4 ± 43.5†

*Significant ($P < .05$) mean differences for father-mother or son-daughter (within-generation) comparisons.

†Significant ($P < .05$) mean differences for father-son or mother-daughter (within-sex) comparisons.

‡46 of 90 mothers were premenopausal.

Data Adjustments

Baseline SHBG levels were adjusted for the effects of a polynomial in age (age, age², and age³) and body mass index (BMI) within each of the 4 sex × generation groups on both the mean and the variance (eg, heteroscedasticity) using a stepwise multiple regression procedure. Baseline SHBG levels were correlated with age in men ($r = .27$, $P = .001$) and with the BMI ($r = -.37$, $P = .001$), estradiol ($r = .17$, $P = .004$), testosterone ($r = -.41$, $P = .001$), and insulin ($r = -.31$, $P = .001$) in men and women in the present study. Therefore, the

baseline was further adjusted for the effects of estradiol, insulin, and testosterone levels. The response to training was adjusted for age (polynomial) and baseline SHBG levels within each of the 4 sex × generation groups, and was additionally adjusted for the effects of the BMI and estradiol, insulin, and testosterone levels. For each of the regressions, only terms that were significant at the 5% level were retained. Each of the adjusted phenotypes used in the genetic analysis was finally standardized to a mean of 0 and a SD of 1.

Familial Resemblance

The computer program SEGPATH[29] was used to fit the sex-specific familial correlation model directly to the family data using the maximum-likelihood method. The general model was based on 4 subgroups (fathers (f), mothers (m), sons (s), and daughters (d)), giving rise to 8 correlations in 3 familial classes (1 spouse (fm), 4 parent-offspring (fs, fd, ms, and md), and 3 sibling (ss, dd, and sd)). Each null hypothesis was tested by comparison to the general model using the likelihood ratio test (LRT), which is the difference in minus twice the log-likelihood ($-2 \ln L$) obtained under the 2 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 non-nested models.[30] The "best" model is the one with the smallest AIC.

The significance of various components of the familial resemblance was examined in models 2 to 4. Sex and generation differences, sex-specific hypotheses, and same-sex versus opposite-sex models were tested in models 5 to 11. Finally, a single correlation was fit to the data by equating all 8 correlations in model 12 (Tables 2 and 3). A parsimonious model was obtained by combining the nonrejected hypotheses into a single test and by the AIC. Maximal heritability was computed using the familial correlations from the most parsimonious model (Table 4). This estimate includes both polygenic and familial environmental sources of variance, and is adjusted for the degree of spouse resemblance.

Segregation Analysis

Segregation analysis, as implemented in the computer program POINTER,[31-33] was performed using the unified mixed model.[34] 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 2 alleles (A and a). The a allele is associated with higher trait values. Included in the model are 7 parameters: (1) the overall variance (V), (2) the overall mean (u), (3) the frequency of the a allele (q), (4) the displacement between the 2 homozygous means (t), (5) the relative position of the heterozygous mean or dominance (d), and (6 and 7) the multifactorial heritability in offspring (H) and in parents (HZ). The transmission pattern of the major gene from parents to offspring is characterized by 3 parameters: (1) τ_1 is the probability that an AA individual transmits allele A to the offspring, (2) τ_2 is the probability that Aa transmits A, and (3) 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 3 τ values are equal, no transmission of the major effect is obtained. The following 3 conditions are usually required to infer a major gene[33]: (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). Competing models are tested for significance using the LRT.

RESULTS

The mean baseline SHBG and the response to training (mean ± SD) are shown in Table 1. Based on a comparison of standard errors (SEs), there were significant sex differences in the mean baseline SHBG, with higher levels in women versus men within generation. While there was no generation difference in mothers and daughters, mean baseline SHBG levels were significantly higher in fathers than in sons. The mean change in response to training was significantly different between fathers and mothers (but not significant between sons and daughters) and between mothers and daughters (but not significant between fathers and sons). For baseline SHBG levels, the percentage of the variance accounted for by other primary parameters was 24% (testosterone and age^3), 38% (estradiol and insulin), 28% (testosterone and insulin), and 22% (BMI, estradiol, and insulin) in fathers, mothers, sons, and daughters, respectively. For the response to training, the percentage of the variance accounted for by other primary parameters was 14% (baseline estradiol), 24% (baseline), 5% (baseline), and 6% (baseline) in fathers, mothers, sons, and daughters, respectively.

Familial correlation model-fitting results are listed in Tables 2 and 3. For the age-BMI–adjusted baseline, all of the constrained models were rejected, and according to the AIC, the general model was the most parsimonious (AIC = 16.0). For the age-BMI-estradiol-insulin-testosterone–adjusted baseline, the significant P values suggested the presence of sibling (model 2), parent-offspring (model 3), and spouse correlations (model 4).

Table 2. Model-Fitting Summary for Baseline SHBG

Model	*df*	Baseline*		Baseline†	
		P	AIC	*P*	AIC
1. General model	0	—	16.0	—	16.0
2. No sibling correlations (ss = dd = sd = 0)	3	<.01	38.2	<.01	48.1
3. No parent-offspring correlations (fs = fd = ms = md = 0)	4	<.01	54.2	<.01	48.3
4. No spouse correlations (fm = 0)	1	<.01	24.7	<.01	28.2
5. No sex differences in offspring (fs = fd, ms = md, ss = dd = sd)	4	<.01	25.5	.09	16.0
6. No sex differences in offspring or parents (fs = fd = ms = md, ss = dd = sd)	5	<.01	26.3	.03	18.7
7. No sex and no generation differences (fs = fd = ms = md = ss = dd = sd)	6	<.01	26.7	.04	17.5
8. Single correlation (fm = fs = fd = ms = md = ss = dd = sd)	7	<.01	26.3	.03	17.2
9. Sex-specific (fd = ms = sd, fs = ss, md = dd)	4	.02	19.8	.01	20.5
10. Sex-specific (spouse included) (fm = fd = ms = sd, fs = ss, md = dd)	5	<.01	22.6	.01	20.7
11. Same sex *v* opposite sex (fd = ms = sd, fs = md = ss = dd)	5	<.01	21.5	.01	21.2
12. Same sex *v* opposite sex (spouse included) (fm = fd = ms = sd, fs = md = ss = dd)	6	<.01	23.1	.86	6.6
Parsimonious					
1.	0	—	16.0		
12.	6			.86	6.6

*Age-BMI–adjusted baseline.

†Age-BMI-estradiol-insulin-testosterone–adjusted baseline.

Table 3. Model-Fitting Summary for SHBG Response to Training

Model	df	Response* P	Response* AIC	Response† P	Response† AIC
1. General model	0	—	16.0	—	16.0
2. No sibling correlations (ss = dd = sd = 0)	3	.02	19.9	.11	16.0
3. No parent-offspring correlations (fs = fd = ms = md = 0)	4	.02	19.6	.07	16.7
4. No spouse correlations (fm = 0)	1	.10	16.8	.25	15.4
5. No sex differences in offspring (fs = fd, ms = md, ss = dd = sd)	4	.10	15.9	.24	13.5
6. No sex differences in offspring or parents (fs = fd = ms = md, ss = dd = sd)	5	.16	14.0	.29	12.2
7. No sex and no generation differences (fs = fd = ms = md = ss = dd = sd)	6	.21	12.5	.38	10.4
8. Single correlation (fm = fs = fd = ms = md = ss = dd = sd)	7	.25	11.1	.45	8.8
Parsimonious					
Single correlation without spouse correlations (fm = 0, fs = fd = ms = md = ss = dd = sd)	7	.14	12.9	.33	10.0
8.	7	.25	11.1	.45	8.8

*Age-baseline–adjusted response to training.

†Age-BMI-estradiol-insulin-testosterone-baseline–adjusted response to training.

Although model 5 (no sex differences in offspring) was not rejected ($P = .09$), models 6 and 7 (no sex and generation differences) and model 8 (a single correlation) were rejected. Sex-specific hypotheses were further tested, and models 9 to 11 were rejected, whereas model 12 (same sex *v* opposite sex, including spouse correlations) was not rejected, which provided the most parsimonious fit according to the AIC (6.6). For the age-baseline–adjusted response to training, there were significant sibling and parent-offspring correlations but no spouse correlations and no sex and generation differences in the correlations. Both hypotheses of a single correlation in the absence and in the presence of spouse correlations were not rejected, and the latter provided the most parsimonious fit according to the AIC (11.1). For the age-BMI-estradiol-insulin-testosterone-baseline–adjusted response to training, none of the constrained hypotheses were rejected, and according to the AIC, the hypothesis of a single correlation in the presence of spouse correlations was the most parsimonious (AIC = 8.8). Parameter estimates (correlations ± SE) are listed in Table 4 under both the general and the most parsimonious models. The maximal heritability estimates, which include both genetic and familial environmental sources of variance, were 50% for the age-BMI–adjusted baseline and reached 64% for the age-BMI-estradiol-insulin-testosterone–adjusted baseline. The estimates were 32% and 25% for the age-baseline– and age-BMI-estradiol-insulin-testosterone-baseline–adjusted response to training.

Results for the segregation analysis are listed in Table 5. For the results from the sample without postmenopausal mothers, only the age-BMI–adjusted baseline and age-baseline–adjusted response to training are presented, because similar patterns of results were obtained from the baseline and response to training data which were additionally adjusted for the effects of estradiol, insulin, and testosterone levels. The parameter estimates under the most parsimonious segregation models are listed in Table 6. For the baseline in the whole sample, the hypotheses of no multifactorial effect (model 2), no major effect (model 3), and no familial effect (model 4) were rejected, suggesting the presence of a multifactorial component and a major effect. Furthermore, the hypothesis of no generation difference in the multifactorial effect was not rejected. Additive (model 7) and dominant (model 8) modes of inheritance were rejected, while the recessive mode (model 6) was not rejected. Tests on the transmission probabilities were performed under the parsimonious Mendelian hypothesis (model 6, a recessive major gene effect with no generation difference in the multifactorial component). The Mendelian τ's (model 9) were rejected while the equal τ's (model 10) were not rejected, and the latter provided the best fit to the data according to the AIC (10.7). The major effect therefore appeared to be nontransmitted and familial environmental in origin. For the baseline in the sample without postmenopausal mothers, there was no major effect but a multifactorial component. The hypothesis of no generation difference in the multifactorial effect was not rejected, and actually provided the best fit to the data according to the AIC (10.5). The heritability estimates were 55% for the age-BMI–adjusted baseline and 61% for the age-BMI-estradiol-insulin-testosterone–adjusted baseline (Table 6).

For the response to training in the whole sample, there were significant multifactorial and major effects, and there was a generation difference in the multifactorial component. While

Table 4. Familial Correlations and Heritability Estimates (±SE) of SHBG

Parameter	Baseline*	Baseline†	Response‡	Response§
General model				
fm	0.44 ± 0.11	0.52 ± 0.10	0.31 ± 0.16	0.23 ± 0.18
fs	0.44 ± 0.08	0.49 ± 0.07	0.26 ± 0.09	0.24 ± 0.09
fd	0.37 ± 0.07	0.39 ± 0.07	0.07 ± 0.09	0.09 ± 0.09
ms	0.07 ± 0.15	0.26 ± 0.11	0.32 ± 0.11	0.22 ± 0.14
md	0.43 ± 0.08	0.28 ± 0.12	0.11 ± 0.10	0.01 ± 0.10
ss	0.48 ± 0.09	0.52 ± 0.08	0.37 ± 0.12	0.30 ± 0.13
sd	0.13 ± 0.11	0.32 ± 0.09	0.11 ± 0.09	0.07 ± 0.09
dd	0.20 ± 0.10	0.16 ± 0.10	0.02 ± 0.09	0.03 ± 0.09
Parsimonious				
fm	0.44 ± 0.11	0.36 ± 0.06	0.17 ± 0.05	0.13 ± 0.05
fs	0.44 ± 0.08	0.40 ± 0.06	[0.17]	[0.13]
fd	0.37 ± 0.07	[0.36]	[0.17]	[0.13]
ms	0.07 ± 0.15	[0.36]	[0.17]	[0.13]
md	0.43 ± 0.08	[0.40]	[0.17]	[0.13]
ss	0.48 ± 0.09	[0.40]	[0.17]	[0.13]
sd	0.13 ± 0.11	[0.36]	[0.17]	[0.13]
dd	0.20 ± 0.10	[0.40]	[0.17]	[0.13]
Heritability	50%‖	64%	32%	25%

NOTE. Values in brackets were equated to a preceding parameter.

*Age-BMI–adjusted baseline.

†Age-BMI-estradiol-insulin-testosterone–adjusted baseline.

‡Age-baseline–adjusted response to training.

§Age-BMI-estradiol-insulin-testosterone-baseline–adjusted response to training.

‖Maximal heritability computed as $\{(r_{sibling} + r_{parent\text{-}offspring})(1 + r_{spouse})/(1 + r_{spouse} + 2 \cdot r_{spouse} \cdot r_{parent\text{-}offspring})\}$, includes both genetic and familial environmental sources of variance, and is adjusted for the degree of spouse resemblance. The estimates were 73% in men, 50% in women, and 31% in men *v* women for age-BMI–adjusted baseline.

Table 5. Segregation Analysis of Baseline SHBG and the Response to Training

Model	*df*	Whole Sample *P*	Whole Sample AIC	Analysis Sample† *P*	Analysis Sample† AIC
Baseline SHBG‡					
1. General Mendelian	0	—	26.2	—	14.0
2. No multifactorial (H = Z = 0)	2	<.01*	47.4	<.05*	16.0
3. No major effect (d = t = q = 0)	3	<.01*	81.1	.73	9.3
4. No familial (d = t = q = H = Z = 0)	5	<.01*	118.1	<.01*	55.4
5. No generation difference (Z = 1)§	1	.53	25.3	.34	10.5
6. Recessive (d = 0, Z = 1)	2	.73	23.6		
7. Additive (d = 0.5, Z = 1)	2	<.01*	56.7		
8. Dominant (d = 1, Z = 1)	2	<.01*	54.9		
9. General (d = 0, Z = 1; τ_1, τ_2, τ_3)	3	<.01*	16.0		
10. No transmission (d = 0, Z = 1; 1 − q)	3	.88	10.7		
SHBG response to training‖					
1. General Mendelian	0	—	16.4	—	18.6
2. No multifactorial (H = Z = 0)	2	.02*	20.7	.03*	21.9
3. No major effect (d = t = q = 0)	3	<.01*	80.2	<.01*	69.9
4. No familial (d = t = q = H = Z = 0)	5	<.01*	93.9	<.01*	77.9
5. No generation difference (Z = 1)	1	.03*	19.2	.27	17.8
6. Recessive (d = 0)¶	1	.51	14.8	.55	15.8
7. Additive (d = 0.5)¶	1	<.01*	53.6	<.01*	72.2
8. Dominant (d = 1)¶	1	<.01*	63.2	<.01*	48.1
9. General (d = 0; τ_1, τ_2, τ_3)¶	3	.43	18.0	.12	16.0
10. No transmission (d = 0; τ's = 1 − q)¶	3	.01*	23.1	.99	10.0

*Statistical significance ($P < .05$).

†The sample without postmenopausal mothers.

‡Age-BMI–adjusted baseline.

§For the sample without postmenopausal mothers, d = t = q = 0, Z = 1, *df* = 4.

‖Age-baseline–adjusted response to training.

¶For the whole sample, Z = 1 (models 6-10), *df* = 2 (models 6-8).

the recessive mode was not rejected, additive and dominant modes of inheritance were rejected. Tests on the transmission probabilities were performed under the parsimonious Mendelian hypothesis (model 6, a recessive major gene effect with a generation difference in the multifactorial component). The Mendelian τ's (model 9) were not rejected, whereas the equal τ's hypothesis was rejected. The AIC suggested that the recessive Mendelian hypothesis (model 6; AIC = 14.8) best fit the data. Therefore, in addition to a multifactorial effect accounting for more variance in parents (52%) than in offspring (8%), a putative major gene accounted for 43% of the variance, with 3% of the sample being homozygous recessive (*aa*) leading to higher values in the response to training. In the sample without postmenopausal mothers, there were multifactorial and major effects without a generation difference in the multifactorial effect. The recessive mode was not rejected, whereas additive and dominant modes of inheritance were rejected. Tests on the transmission probabilities were performed under the parsimonious Mendelian hypothesis (model 6, a recessive major gene effect without a generation difference in the multifactorial component). Neither the Mendelian τ's nor the equal τ's hypothesis was rejected, and the AIC suggested that the nontransmitted hypothesis (model 10; AIC = 10.0) best fit the data. Therefore, in addition to a multifactorial component (21% and 17% for the age-baseline– and age-BMI-estradiol-insulin-testosterone-baseline–adjusted response to training, respectively), the results suggest that there is a major effect (accounting for 31% and 36% of the variance for the age-baseline– and age-BMI-estradiol-insulin-testosterone-baseline–adjusted response to training, respectively) which is not transmitted in families.

DISCUSSION

This study reports the familial resemblance (due to both multifactorial and major gene sources) for baseline SHBG levels and the response to a 20-week endurance exercise training program in 99 sedentary white families. Since the physical activity level was controlled for at baseline, it is interesting to compare heritabilities from these physically inactive families with findings from other heterogeneous samples, which presumably include a mixture of physically active and inactive families.

Table 6. Parsimonious Segregation Models for Baseline SHBG and the Response to Training (d = 0)

SHBG	t	q	H	Z	%*	q^2
Baseline†	2.54 ± 0.12	0.30 ± 0.02	0.34 ± 0.04	[1]	45%	9%
Baseline‡	[0]	[0]	0.55 ± 0.06	[1]	0%	0%
Baseline§	[0]	[0]	0.61 ± 0.06	[1]	0%	0%
Response‖	4.94 ± 0.62	0.18 ± 0.03	0.08 ± 0.02	6.50 ± 1.97	43%	3%
Response¶	4.61 ± 0.38	0.15 ± 0.02	0.21 ± 0.05	[1]	31%	2%
Response#	4.18 ± 0.31	0.18 ± 0.02	0.17 ± 0.06	[1]	36%	3%

*Percentage accounted for by major effects.

†Age-BMI–adjusted baseline in the whole sample, no transmission ($\tau_1 = \tau_2 = \tau_3 = 0.70$).

‡Age-BMI–adjusted baseline and §Age-BMI-estradiol-insulin-testosterone–adjusted baseline in the sample without postmenopausal mothers.

‖Mendelian transmission ($\tau_1 = 1$, $\tau_2 = 0.5$, $\tau_3 = 0$) for the age-baseline–adjusted response to training (H = 8%, HZ = H × Z = 52%) in the whole sample.

¶No transmission ($\tau_1 = \tau_2 = \tau_3 = 0.85$) for the age-baseline–adjusted response to training and #no transmission ($\tau_1 = \tau_2 = \tau_3 = 0.82$) for the age-BMI-estradiol-insulin-testosterone-baseline–adjusted response to training in the sample without postmenopausal mothers.

Several other hormones appear to be correlated with SHBG levels. For instance, it has been reported that estradiol significantly increases SHBG, and in contrast, insulin and testosterone decrease SHBG.[24-26] In the present study, estradiol levels ($r = .17$, $P = .004$) were positively associated with SHBG levels, whereas insulin ($r = -.31$, $P = .001$) and testosterone ($r = -.41$, $P = .001$) were negatively associated with SHBG levels. Therefore, the heritabilities were assessed by further adjustments for the effects of estradiol, insulin, and testosterone levels in the sample without postmenopausal mothers (their hormone levels significantly decreased, and they may have received hormone replacement therapy for menopause). A significant maximal heritability (50%) for the age-BMI–adjusted baseline SHBG was found in the current study. Interestingly, the estimate reached 64%, independent of the effects of age, sex, BMI, and estradiol, insulin, and testosterone levels. In general, our estimates are higher than that (31%) for SHBG levels measured using a radioimmunometric procedure from a previous report in Mexican-Americans participating in the San Antonio Family Heart Study,[17] suggesting additional/stronger familial impacts on the variation of SHBG levels in the sedentary HERITAGE families. In addition to possible race differences in the genetic component and familial environments between the samples, the HERITAGE Family Study may also be more homogeneous since the physical activity level was controlled for at baseline. It is interesting to note that Meikle et al[14] found a significant heritability estimate (62%, comparable to 64% in this study) in a recent twin study when SHBG was analyzed specifically by a radioimmunometric procedure rather than a competitive protein binding technique.[15-16] The latter technique resulted in either no familiality[11] or negligible heritability ($\leq 5\%$)[12,13] in 3 previous twin studies.

SHBG transports sex hormones, and therefore, the circulating serum SHBG levels might be regulated differently in men and women. Consistent with this sex difference in regulation, we observed significantly higher baseline SHBG levels in women versus men and a sex difference in the maximal heritability (73% in men and 50% in women) in this study. A previous study proposed but obtained no evidence that genetic and familial environmental influences on SHBG levels differed in men and women.[17] The maximal heritability for the SHBG response to training (independent of baseline SHBG levels) reached 32% without a sex difference (25% when the data were further adjusted for the effects of BMI, estradiol, insulin, and testosterone levels) in the current study. Because the effects of baseline SHBG levels were removed from the response to training (via regression analysis), the familial influences on the SHBG response to training are probably different from those for baseline SHBG levels. We are aware of no previous reports on the familial aggregation of SHBG in response to training.

In the current study, spouse correlations were notable (.44 for the baseline). In contrast to parent-offspring and sibling correlations, spouse resemblance may be primarily explained by shared environmental factors. The heritability estimates for SHBG were adjusted for the level of spouse resemblance assuming that the latter is nongenetic in this study. However, assortative mating for fatness, dietary preferences, sedentary, and other potential life-style factors may also contribute to the appreciable spouse resemblance in SHBG levels. One might expect that the type of food or caloric content ingested might correlate between spouses, and thus the degree of obesity and SHBG levels. However, in the present study, the data did not support a correlation for BMI between fathers and mothers ($r = -.02$, $P = .88$).

Segregation analysis suggested that baseline SHBG levels were influenced by a multifactorial component (heritability 29%), as well as a major effect which was not transmitted in families, accounting for an additional 45% of the variance. These findings suggested that the familial etiology of baseline SHBG is predominantly multifactorial. The non-Mendelian nature of the major effect may be a function of specific environmental factors. However, an alternate explanation is that the major effect is due to multigenic factors. Bérubé et al[18] located the SHBG structural gene on human chromosome 17p12-13. Moreover, other unidentified loci may be involved in SHBG regulation.[17] A recent report suggested that SHBG regulates sex steroid action at the tissue level (eg, estrogen target cells such as epithelial, stromal, and muscle cells in the human Fallopian tube which contain the estrogen receptor).[35] Together, these reports suggest that the non-Mendelian major effect noted here is due to the influence of several interacting loci (ie, oligogenic or multigenic). In contrast to the baseline results, clear evidence of a major gene effect was revealed for the response to training along with a multifactorial component (the latter accounted for more variance in the parents (52%) *v* the offspring (8%)). The Mendelian gene exhibited a recessive mode of inheritance, and its effect accounted for 43% of the variance. An estimated 3% of the sample was homozygous for the "high" genotype. It should be noted that the major effect for the baseline and the major gene effect for the response to training were undetectable in the sample without postmenopausal mothers. This pattern of results would suggest a cautious interpretation of the major gene effect for the response to training, because not only a reduced sample size but also some possible confounding effects arising from the postmenopausal mothers' being characterized by significantly decreased sex hormone levels might account for this perplexing observation.

It is not unexpected in the current study that the mean changes in SHBG levels in response to training in each of the 4 sex × generation subgroups (fathers, premenopausal mothers, sons, and daughters) were either very modest or close to zero. The response to training may cluster in families, and thus, we cannot conclude that there is no familiality just because the overall mean change of SHBG levels in response to training is near zero. In fact, both familial aggregation and segregation analysis results from this study consistently support a significant familial (genetic and/or environmental) effect for the response to training.

In conclusion, in a sample of 99 white families in the HERITAGE Family Study, baseline SHBG levels and the response to endurance training were determined in part by genetic and possible familial environmental factors with a sex difference for the baseline. In addition, the response to training was influenced by a putative major recessive gene, which may provide the basis to search for candidate genes using genome-wide linkage scans and association methodologies.

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