Race Differences in the Pattern of Familial Aggregation for Dehydroepiandrosterone Sulfate and Its Responsiveness to Training in the HERITAGE Family Study

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Using a familial correlation model to assess familial influences, baseline dehydroepiandrosterone sulfate (DHEAS) and its change (post-training minus baseline) in response to a 20-week endurance exercise training program were analyzed in 85 black families who participated in the HERITAGE Family Study (HERITAGE). Baseline levels were adjusted for a polynomial in age, and the training response was adjusted for a polynomial in age, as well as the baseline values, within 4 sex-by-generation groups before genetic analysis. We found that the maximal heritability for baseline DHEAS reached 66% (with no sex and generation differences) in black families, which is slightly (but not significantly) higher than the estimate (58%) reported previously in 99 white families in HERITAGE. Whereas weak, but significant, familial effects (26%) for the training response were previously reported for whites in HERITAGE, they were undetectable in the present study. Furthermore, we found heterogeneity in the pattern of familial aggregation (primarily due to different spouse and parent-offspring correlations) for both the baseline and its training response between blacks and whites. In conclusion, baseline DHEAS levels in blacks were also determined by substantial familial factors (just as for whites), independent of the effects of age and sex. Genetic and nongenetic familial components influencing baseline DHEAS levels in both races may be different.

DEHYDROEPIANDROSTERONE (3β-hydroxyandrost-5-ene-17-one, DHEA) 3-sulfoconjugate (DHEAS) is the principal C-19 steroid produced in high quantities by the human adrenal glands, with higher levels in men than in women after puberty.[1,2] In distinct contrast to other adrenal steroids, DHEAS levels decline progressively and markedly with aging.[1,3,4] In men, epidemiologic reports have consistently suggested that low DHEAS levels are associated with an increased risk for cardiovascular disease (CVD) and diabetes.[5-7] Interestingly, high levels of DHEAS appear to confer beneficial effects against the development of degenerative processes.[4] Results in women, however, suggest that high levels of DHEAS may either indicate increased risk of mortality from CVD[8,9] or have no effect.[10,11] In addition, DHEAS may be a metabolic precursor of testosterone and estradiol in women[2,12] and is associated with levels of testosterone, estradiol, sex hormone-binding globulin (SHBG), insulin, and numerous CVD risk factors.[4,13]

Previous twin and family studies found that DHEAS levels were under the influences of genetic determinants and familial environmental factors, with the magnitude of the effect ranging from 39% to 65%.[14-17] Sex differences in the familiality were shown in white families who participated in the Cincinnati Myocardial Infarction and Hormone (CIMIH) Family Study[18] and in the HERITAGE Family Study (HERITAGE),[19] in which the maximal heritabilities reached 65% in men and 50% in women.[19]

It is not clear if regular exercise has any chronic effect on DHEAS concentrations. Two studies suggested that DHEAS levels increased after exercise training,[20,21] whereas 1 investigation questioned whether exercise training alone could affect DHEAS levels.[22] To address changes in DHEAS levels in response to training (post-training minus baseline), it is necessary to note that the metabolic clearance rate of DHEAS is very low (about 13.8 L/day in men and 12.5 L/day in women) due to its strong binding to albumin.[12] HERITAGE is the only study that has explored a familial basis for its training response, and the maximal heritability was 26% in white participants.[19]

DHEAS levels are slightly higher in preteen blacks than whites, which may be due to an earlier onset of adrenarche in black children. The racial difference, however, is either minimal or nonsignificant in older children and adults.[23,24] None of the previous genetic analyses were performed in blacks. This study not only represents our first attempt to delineate familiality in black individuals, but also provides an opportunity to assess heterogeneity in the pattern of familial aggregation between the 2 races. Recruitment of eligible HERITAGE families, a selected sample, is based on extensive publicity and advertisement efforts. HERITAGE is unique in that DHEAS levels were assessed before and following a 20-week endurance exercise training program in intact families. Initial physical activity level was controlled for by requiring all participants to be sedentary at baseline, ie, not engaging in regular vigorous

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physical activity over the previous 6 months (see Bouchard et al,[25] for details).

MATERIALS AND METHODS

Sample

HERITAGE 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 CVD and diabetes risk factors. A description of HERITAGE protocol, population, and inclusion and exclusion criteria has been published elsewhere.[25]

A total of 296 individuals from 85 black families (109 men and 187 women) and 472 individuals from 99 white families (233 men and 239 women) completed the training. Participants with incomplete pre- and post-training DHEAS measurements were excluded for the training response. Table 1 gives the sample sizes within 4 sex-by-generation groups (fathers, mothers, sons, and daughters) and by the races (blacks and whites) for the baseline and the training response.

The following entry criteria were applied to screen subjects for participation. First, individuals were between the ages of 17 to 65 years (17 to 40 years for children and $\leq$ 65 years for parents). Second, all participants were required to be sedentary at baseline. Third, a body mass index (BMI) of less than 40 kg/m^2 was required unless a physician certified that the subject was able to safely meet the demands of the exercise testing and training program. Fourth, resting blood pressure (BP) levels were $\leq$ 159 mm Hg for systolic BP and $\leq$ 99 mm Hg for diastolic BP in the absence of medications. Finally, participants were required to be in good general physical health to complete the 20-week exercise training program. Exclusion criteria can be found in a previous publication.[25]

Exercise Training Program

Following the initial test battery, subjects completed a 20-week endurance training program (3 days/week for a total of 60 exercise sessions) on cycle ergometers (Universal Aerobicycle; Cedar Rapids, IA), which were computer-controlled to maintain the participant's heart rate at levels associated with fixed percentages of their $\dot{V}O_2$max. The training program started at 55% of $\dot{V}O_2$max for 30 minutes/session and gradually increased to 75% of $\dot{V}O_2$max for 50 minutes/session during the last 6 weeks of training. The full test battery was administered again at the conclusion of the training program. Details of the training program have been published elsewhere.[26] All training sessions were supervised on site, and adherence to the protocol was strictly monitored.

Measurements

Before and after the 20-week standardized exercise training program, blood samples were taken from an antecubital vein into vacutainer tubes containing EDTA. Samples were collected in the morning after a 12-hour fast with the participant in a semirecumbent position and were drawn twice before training (24 hours apart) and twice near the end of training (at least 24 hours apart and at least 20 hours after a training session). Blood samples collected at each clinical center were prepared according to a standard protocol before being shipped to the core laboratory in Québec. They were adjusted for possible post-training hemodilution based on the assay of total protein. Serum DHEAS concentrations were determined by a specific radioimmunoassay using Diagnostic Products kits (San Antonio, TX). The antiserum is highly specific to DHEAS with very low cross-reactivity to other blood compounds. No effects of bilirubin and hemolysis on the assay were found to be significant.

Baseline DHEAS levels were determined by averaging the 2 pretraining measurements. The training response was determined by a simple difference of the averaged values of the post- and the averaged values of the pretraining levels. Reproducibility of the baseline DHEAS measurements in HERITAGE was very high, with intraclass correlation (ICC) and coefficient of variation (CV) for repeated measurements for day-to-day variation being about 0.96 and 16%, respectively. ICC and CV for analytical error were 0.98% and 10%, respectively.

Data Adjustments

As baseline DHEAS data were not normally distributed, they were log-transformed and adjusted for a polynomial in age (age, age^2, age^3). The adjustments were performed within each of the 4 sex-by-generation groups in both the mean and the variance (eg, heteroscedasticity) using a stepwise multiple regression procedure. The training response was adjusted for a polynomial in age and the baseline values. 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 zero and a standard deviation (SD) of 1.

Familial Resemblance

A sex-specific familial correlation model was used to look for evidence of familial effects underlying the variation in the baseline and the training response. The computer program SEGPATH[27] 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, md*), and 3 sibling (*ss, dd, sd*)). Each null hypothesis was tested by a 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 2 nested 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.[28] The most parsimonious model is the one with the smallest AIC.

The null hypotheses of no sex and generation differences were tested in model 2 (no sex differences in offspring, $fs=fd$, $ms=md$, $ss=dd=sd$), model 3 (no sex differences in parents or offspring, $fs=fd=ms=md$, $ss=dd=sd$), and model 4 (no sex or generation differences, $fs=fd=ms=md=ss=dd=sd$) (Table 2). The significance of the familial correlations was examined in model 5 (no sibling resemblance, $ss=dd=sd=0$), model 6 (no parent-offspring resemblance, $fs=fd=ms=md=0$), and model 7 (no spouse resemblance, $fm=0$). Finally, a single correlation was fit to the data by equating all 8 parameters in model 8. A parsimonious model was determined by combining as many of the nonrejected hypotheses into a single test as possible. Maximal heritability was computed using the familial correlations from the most parsimonious model. This estimate includes both polygenic and familial environmental sources of variance and is adjusted for the degree of spouse resemblance (see Table 3 footnote for the equation).

Heterogeneity between the races was tested under a 16-correlation model. This model is a simple extension of the 8-correlation (*fm, fs, fd, ms, md, ss, dd, sd*) model and allows for race-specific correlations (fm_1, fs_1, fd_1, ms_1, md_1, ss_1, dd_1, sd_1 in blacks, and fm_2, fs_2, fd_2, ms_2, md_2, ss_2, dd_2, sd_2 in whites). Because means and variances are estimated separately for each race, this procedure allows for not only testing the overall heterogeneity, but also a determination of the sources of heterogeneity, if any.

RESULTS

Means and SD of the baseline and the training response are given in Table 1. Based on a comparison of standard errors

Table 1. Means and SD for Baseline DHEAS and Its Training Response (ΔDHEAS) in Both Races

Variables	No.	Means	SD	No.	Means	SD
		Fathers			Mothers	
Blacks						
Age (yr)	28	50.2*†	7.2	56	46.4*†	6.7
BMI (kg/m^2)	28	27.3	5.1	56	28.9	4.9
DHEAS (nmol/L)	28	3263†	1784	56	2591†	1450
ΔDHEAS (nmol/L)	25	267†	701	49	−26	942
		Sons			Daughters	
Age (yr)	81	27.3†	7.3	131	27.1†	7.3
BMI (kg/m^2)	81	27.3	5.7	131	27.8	7.1
DHEAS (nmol/L)	81	6730*†	2505	131	4653*†	3231
ΔDHEAS (nmol/L)	61	−573†‡	1443	100	−215	1101
Whites		Fathers			Mothers	
Age (yr)	94	53.4†	5.5	87	52.2†	5.1
BMI (kg/m^2)	94	28.3†	4.5	87	27.1†	4.3
DHEAS (nmol/L)	94	3627*†	2154	87	2263*†	1325
ΔDHEAS (nmol/L)	93	89	702	87	45	549
		Sons			Daughters	
Age (yr)	139	25.5†	6.1	152	25.5†	6.6
BMI (kg/m^2)	139	25.7*†	4.9	152	23.4*†	4.1
DHEAS (nmol/L)	139	7477*†	3331	152	4524*†	2258
ΔDHEAS (nmol/L)	139	−45‡	1600	149	−129	1264

* 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.

‡ Significant ($P < .05$) mean difference between blacks and whites for son-son comparison for the training response.

(SE), there were significant sex and generation differences at baseline, with higher levels in men than in women within generation (nonsignificant for father-mother comparison in the black sample) and with higher levels in offspring than in parents within the same sex. In contrast, no sex or generation differences in the training response were found (except for father-son comparison in the black sample). In addition, no sample difference (between the races) in the baseline or training response was observed (except for son-son comparison for the training response). In black participants, the significant terms and percentages of variance accounted for by the covariates were 19% (baseline) in sons and 5% (age, age^2, age^3) in daughters for the training response. A similar set of stepwise regressions were also performed by including BMI as a covariate, however, it was not a significant predictor of either the baseline or the training response.

Familial correlation model-fitting results for black participants are given in Table 2. For the baseline, rejected hypotheses suggested the presence of sex and generation differences in the familial correlations. Sibling (model 5) and parent-offspring (model 6) correlations were significant, but there was no spouse resemblance (model 7). Both a single correlation (model 8) and a single correlation with no spouse correlation (model 9, *fm=0, fs=fd=ms=md=ss=dd=sd*) hypotheses fit the data. The AIC suggests that the latter is the most parsimonious (AIC = 10.45).

For the training response, none of the constrained models was rejected. The general model did not converge, thus a revised model with no sex difference in the sibling correlations was regarded as the "general: model (see Table 2 footnote), which was used to test each of the constrained hypotheses. A no correlation (model 9, *fm=fs=fd=ms=md=ss=dd=sd=0*) hy-

Table 2. Model-Fitting Summary for Baseline DHEAS and Its Training Response in Blacks

Models	*df*	*P*	AIC
Baseline DHEAS			
1. General model	0	—	16.00
2. No sex differences in offspring	4	.09	15.96
3. No sex differences in parents and offspring	5	.14	14.24
4. No sex and generation differences	6	.21	12.34
5. No sibling correlations	3	<.01	32.75
6. No parent-offspring correlations	4	<.01	23.07
7. No spouse correlation	1	.14	14.14
8. Single correlation	7	.12	13.54
9. Single correlation with no spouse correlation	7	.30	10.45
Training response			
1. General model*	0	—	12.00
2. No sex differences in offspring	2	.56	9.17
3. No sex differences in parents and offspring	3	.54	8.15
4. No sex and generation differences	4	.63	6.61
5. No sibling correlations	1	.34	10.92
6. No parent-offspring correlations	4	.70	6.17
7. No spouse correlation	1	.25	11.30
8. Single correlation	5	.62	5.49
9. No correlation	6	.68	4.01

* The general model did not converge for the training response. It was thus revised (*fm, fs, fd, ms, md, ss = dd = sd*) to test each of the constrained hypotheses.

pothesis fit the data and was the most parsimonious according to the AIC (4.01).

Parameter estimates (correlations ± SE) are given in Table 3 under the general and most parsimonious models. The maximal heritabilities include both genetic and nongenetic familial sources of variance. In contrast to zero for the training response, the heritability for the baseline reached 66%, with no sex and generation differences. Figure 1 presents familial correlation estimates for the baseline in both race groups.

Race differences in familiality were assessed using the 16-correlation heterogeneity model. There were overall heterogeneities between the races in the baseline and training response correlations. Furthermore, they appeared to be primarily due to differences in the spouse and parent-offspring correlations ($P < .05$).

DISCUSSION

The maximal heritability, corrected for the observed degree of spouse resemblance, reached 66% in black families for baseline DHEAS, independent of the effects of age and sex. However, it was zero for the training response, which was similarly corrected for the effects of age and sex, as well as the baseline values. The familial effects in the present study reflect both genetic determinants and shared environmental factors. Familial aggregation studies were previously performed in white twins[14,15] and families,[18,19] as well as Mexican Americans,[16,17] but not in blacks. Therefore, the current report based on black families in HERITAGE conveys new information.

The maximal heritability (66%) for baseline DHEAS in black families was slightly (but not significantly) higher than our estimate (58%) reported previously in white families in HERITAGE.[19] In contrast to sex differences previously shown in whites in HERITAGE,[19] no sex and generation differences in the familial correlations were found in blacks in the current study. This may suggest different familial components between the races. Familial effects for the training response are low in whites (26%), with no sex and generation differences in the correlations.[19] They were, however, undetectable in blacks in the present study. In the literature, either no sex differences in familiality were reported in the San Antonio Family Heart Study (SAFHS),[16] or they had an opposite pattern, ie, higher estimates in women (74%) than in men (29%) in the CIMIH Family Study,[18] suggesting possible differences in characteristics of the samples. In HERITAGE, participants were sedentary, healthy, nonobese, nondiabetic, and nonhypertensive, whereas in the CIMIH Family Study, the families were ascertained through white men who survived a myocardial infarction before the age of 56.[18,19] The participants in the SAFHS were low income Mexican Americans and were randomly ascertained without regard to disease status.[16]

Our estimate (66%) for baseline DHEAS in black families is also somewhat higher than (or as high as) those (39% to 65%) from other studies in whites and Mexican Americans.[14-18] Although circulating DHEAS levels are not significantly different between blacks and whites in adulthood,[23,24] the heritability could still vary across the races. In the present study, an in-depth assessment of heterogeneity in the familial correlations between the races not only evidenced overall sample heterogeneity, but also pointed to differences in spouse and parent-offspring correlations at baseline and in response to training. The correlation estimates were different (borderline to significant, $P \leq .05$) between the races in spouse (zero in blacks *v* 0.27 ± 0.10 in whites), father-daughter (0.33 ± 0.05 in blacks *v* 0.21 ± 0.08 in whites), mother-son (0.33 ± 0.05 in blacks *v* 0.24 ± 0.09 in whites), son-daughter (0.33 ± 0.05 in blacks *v* 0.47 ± 0.12 in whites), and daughter-daughter (0.33 ± 0.05 in blacks *v* 0.20 ± 0.09 in whites) correlations in HERITAGE. In contrast, the estimates were similar for father-son (0.33 ± 0.05 in blacks *v* 0.34 ± 0.08 in whites), mother-

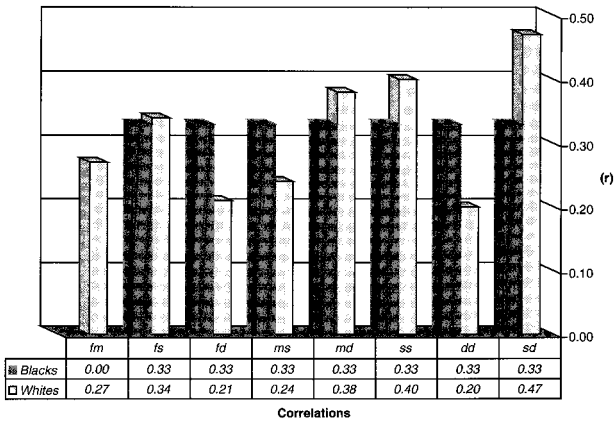

Fig 1. Differences in familial correlations for baseline DHEAS between blacks and whites in the HERITAGE Family Study.

Table 3. Maximal Heritabilities (±SE) for Baseline DHEAS and Its Training Response in Blacks

Parameters	General Model	Parsimonious Model
Baseline DHEAS		
fm	0.06 ± 0.17	[0]*
fs	0.57 ± 0.14	0.33 ± 0.05
fd	0.27 ± 0.15	[0.33]
ms	0.24 ± 0.15	[0.33]
md	0.32 ± 0.11	[0.33]
ss	0.62 ± 0.12	[0.33]
dd	0.41 ± 0.11	[0.33]
sd	0.08 ± 0.18	[0.33]
Maximal heritability (%)†		66 ± 10
Training response		
fm	0.25 ± 0.20	[0]
fs	0.32 ± 0.31	[0]
fd	0.07 ± 0.18	[0]
ms	0.06 ± 0.18	[0]
md	−0.26 ± 0.20	[0]
ss	0.11 ± 0.12	[0]
dd	[0.11]	[0]
sd	[0.11]	[0]
Maximum heritability (%)		0

* Parameters in square brackets were fixed to zero or equated to a preceding parameter.

† Maximal heritability computed as $[(r_{sibling} + r_{parent\text{-}offspring})(1 + r_{spouse})/(1 + r_{spouse} + 2*r_{spouse}* r_{parent\text{-}offspring})]$ includes both genetic and familial environmental sources of variance and is adjusted for the degree of spouse resemblance.[29]

daughter (0.33 ± 0.05 in blacks *v* 0.38 ± 0.07 in whites), and son-son (0.33 ± 0.05 in blacks *v* 0.40 ± 0.10 in whites) correlations between the races (see Fig 1). Although a similar analysis was not performed in blacks previously, we noted 1 report in white families in the Cincinnati Myocardial Infarction and Hormone Family Study.[18] In that study, the son-son (0.15 ± 0.07) and daughter-daughter (0.37 ± 0.05) correlations showed an opposite pattern of sex differences in familial correlations than those in whites in HERITAGE, while the spouse and parent-offspring correlations were quite compatible with those in white families in HERITAGE. The observed sex differences in familial correlations appear to be due to differences in the specific characteristics of the samples.

In conclusion, baseline DHEAS in HERITAGE black participants is under the influence of substantial genetic determinants and nongenetic familial factors, with no sex and generation differences. Heterogeneity in the pattern of familial aggregation between the races was found, which was mainly driven by different spouse and parent-offspring correlations. Familial effects on the training response are negligible in blacks, while they are low in whites.

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