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Genetic determination of adiponectin and its relationship with body fat topography in multigenerational families of African heritage

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Abstract

Adiponectin, an adipose-specific protein, is negatively associated with adiposity, insulin sensitivity, and diabetes. Very few studies have examined the role of heredity in the regulation of adiponectin and its association with body fat among individuals of African heritage. Thus, we measured fasting serum adiponectin levels by radioimmunoassay and body composition by dual-energy x-ray absorptiometry (DEXA) in 402 individuals aged 18 to 103 years belonging to 7 multigenerational families of African heritage in the relatively homogeneous island population of Tobago. Heritability of adiponectin was 33.2% ($P < .01$), and age, sex, and body mass index explained 23.4% of the variance in adiponectin. Sex-specific heritability was significant in men (heritability, 34%; $P < .05$), but not in women. The inverse associations between body mass index and percentage of body fat and adiponectin, independent of age and height, were much stronger in women (all P values $<.001$) than in men. However, percentage of trunk fat was consistently strongly associated with adiponectin in both men ($r = -0.40$, $P < .001$) and women ($r = -0.44$, $P < .001$), independent of age and height. This study suggests that genetic factors are a significant source of interindividual differences in circulating adiponectin among Afro-Caribbeans. Adiponectin may serve as a promising quantitative intermediate trait in studies designed to map the genes underlying diabetes and obesity in this population.

1. Introduction

Adiponectin is a hormone secreted by adipocytes. Adiponectin may play a role in obesity by promoting fatty acid oxidation [1] and is inversely associated with body mass index (BMI) [2] and subcutaneous abdominal and intra-abdominal fat tissue [2]. Adiponectin can also increase insulin sensitivity in peripheral tissues such as skeletal muscle and liver, promotes glucose uptake [3], and has been associated with the risk for a number of obesity-related diseases, such as diabetes [4], hypertension [5], and coronary heart disease [6]. Recently, it was reported that adiponectin may be an inherited survival factor in exceptional longevity [7]. Furthermore, sex and ethnic differences in adiponectin levels have been reported. Levels of adiponectin are higher in women than in men [2], and adiponectin levels are reported to be lower in Pima Indians [8], Asian-Indians [9,10], and African Americans [11-14] compared with whites.

There have been only a few studies of the familial aggregation of adiponectin. These studies revealed a substantial variability in heritability estimates, for example, from 30% in Italian families [15], 39% in Pima Indians [16], 48% in Japanese [17], 70% in Chinese [17], 82% in African Americans [18], to 93% in Hispanic children [19]. No studies have been conducted in populations of African descent outside the United States. Thus, we determined the extent to which genes (heredity) and environmental factors might contribute to serum adiponectin levels within families of African descent.

2. Methods

In 2003, we began the Tobago Family Health Study on the Caribbean island of Tobago to better understand the role of

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Table 1
Characteristics of the study participants

	Men (n = 157)	Women (n = 245)
Age (y)	42.1 ± 16.8	42.6 ± 17.4
Current smoking* (%)	13.6	0.37
Alcohol use* (%)	27.5	2.1
Time spent walking per week (min)	50.4 ± 69.1	46.4 ± 119.9
Use of oral contraceptives (%)	N/A	32.1
Postmenopausal status (%)	N/A	29.2
Waist circumference (cm)	90.2 ± 12.6	90.0 ± 17.0
Height* (cm)	177.1 ± 7.5	166.7 ± 6.6
Weight (kg)	84.1 ± 17.9	80.9 ± 19.9
BMI* (kg/m^2)	26.8 ± 5.1	29.2 ± 7.1
% Total body fat*	18.9 ± 6.8	35.2 ± 7.9
% Trunk fat*	45.0 ± 5.0	41.8 ± 5.5
History of diabetes (%)	7.0	11.0
Adiponectin* (μg/mL)	7.8 ± 3.6	10.9 ± 5.0

Values are expressed as mean ± SD.
* $P < .05$ for sex difference.

inheritance, lifestyle, and body composition in the etiology of several common chronic diseases including diabetes, obesity, and cardiovascular disease. The population of Tobago is predominantly of West African origin with low non-African admixture. Previous studies in this population with ancestry-informative molecular markers have shown that Afro-Caribbean population of Tobago has considerably less European admixture (6% [20]) compared with the more genetically heterogeneous African American population who has much higher degree of European admixture (17%-23.9% [21-23]). To date, we have recruited 431 individuals aged 18 to 103 years (mean age, 42 years) belonging to 7 multigenerational families of African origin (median family size, 48 individuals; range, 21-112; 3426 relative pairs). To be eligible, a proband had to be Afro-Caribbean, have had a spouse who was willing to participate in the study, and have at least 6 living offspring and/or siblings 18 years and older who were residing in Tobago. Participants were defined as Afro-Caribbean if they reported that all 4 of their grandparents are Afro-Caribbean. Because we were interested in establishing a community-based sample of families, probands and their family members were recruited without regard to their health status. Adiponectin data were available for 402 of 431 participants. Written informed consent was obtained from every participant.

We assessed a number of characteristics of probable importance for adiponectin metabolism, such as standard anthropometry (weight and height) and body composition (dual energy x-ray absorptiometry, Hologic QDR 4500W Scanner [Hologic, Inc, Bedford, MA]; total body fat, percentage of body fat, total body bone-free lean mass, body fat stored in the trunk, and percentage of body fat stored in the trunk [% trunk fat]). Height was measured to the nearest 0.1 cm using a wall-mounted stadiometer. Weight was recorded to the nearest 0.1 kg without shoes on a balance-beam scale. Information on a wide range of lifestyle habits (smoking status, alcohol intake, oral contraceptive use, physical activity [minutes per week]), postmenopausal status, presence of type 2 diabetes (defined as fasting glucose level =126 mg/dL or currently taking diabetes medication), medication use, and reproductive characteristics were also assessed using standardized interviewer-administered questionnaires. We recorded minutes walked per week because walking is the predominant form of physical activity on the island.

Adiponectin concentrations were measured in serum collected between 8:00 and 10:00 AM, after an overnight fast with a commercial radioimmunoassay developed by Linco Research (St Charles, MO). Serum samples were frozen at −80°C until adiponectin determination. The coefficient of variation between runs was 8.0%.

2.1. Statistical analyses

We first determined potential environmental covariates (age, sex, BMI, waist circumference, time spent walking per week, current smoking, alcohol use, use of oral contraceptives) for adiponectin by both forward and backward stepwise regression using the statistical package R (R, Version 2.1.0; R Foundation for Statistical Computing, Vienna, Austria) [24] and a threshold of $P < .05$. Estimates of the mean, variances, and covariate effects were obtained using maximum likelihood methods. Maximum likelihood estimation is applied to a mixed-effects model that includes fixed covariate effects, additive polygenic genetic effects, and residual error. Initial descriptive data analysis showed that adiponectin exhibited markedly skewed distribution. Therefore, before statistical analysis, we transformed adiponectin by natural logarithm to reduce the nonnormality of the distribution. Heritability was estimated simultaneously along with the environmental effects. Heritability was calculated as the additive genetic component (this assumes there is no gene-gene interaction) of variance (or polygenic component) from the covariance among relatives by using the SOLAR (Solar, Version 2.1.4; Southwest Foundation for Biomedical Research, San Antonio, TX) program [25]. Only age, sex, and BMI were found to be significant environmental factors for adiponectin levels, and, therefore, were incorporated into the final heritability estimate model. Our heritability estimates describe the narrow-sense heritability, a direct ratio of variation due to genetics to the total phenotypic variation. The unadjusted and adjusted phenotypic correlation analyses were first performed by using R,

Table 2
Phenotypic correlation (ρ_p[a]) between body composition measurements and adiponectin in the total sample and by sex

	Total sample	P	Men	P	Women	P
BMI[b]	−0.30	<.001	−0.15	.06	−0.38	<.001
% Body fat[c]	−0.25	<.001	−0.11	.20	−0.34	<.001
% trunk fat[d]	−0.42	<.001	−0.40	<.001	−0.44	<.001

[a] Spearman correlation coefficients.
[b] Adjusted for age (+ sex in total sample).
[c] Adjusted for age and height (+ sex in total sample).
[d] Adjusted for age, height, and total lean mass (+ sex in total sample).

Table 3
Components of variance in serum adiponectin levels in Afro-Caribbean families

	Total sample[a] (N = 402)	By sex[b]	
		Men (n = 157)	Women (n = 245)
Covariates (%)[c]	23.4	5.0	17.0
h^2 (%)[d]	33.2**	32.0*	17.0
Residual error (%)[e]	43.4	63.0	66.0

h^2 indicates heritability.
[a] Adjusted for age, sex, and BMI.
[b] Adjusted for age and BMI.
[c] Proportion of variance explained by significant covariates.
[d] Proportion of variance due to additive genetic components—heritability (narrow sense).
[e] Proportion of variance due to unmeasured covariates, unspecified factors, or system errors.
* $P < .05$.
** $P < .01$.

ignoring the non-independence of the subjects within each family. However, we subsequently performed the same analysis limited to the 86 unrelated individuals (78 married-in plus 7 founders from pedigrees). Correlation coefficients were compared between these 2 analyses and found to be similar. Thus, we present the correlation coefficients for the entire data set. Univariate regression analysis by SOLAR was performed (regress the interested variables by sex) to assess differences in measured variables between men and women. This method could account for the dependence of the family data and provide the more stringent P value.

3. Results

Characteristics of the study participants are shown in Table 1. Men and women had similar physical activity levels and history of diabetes, although more men than women smoked or drank alcohol. Men were significantly taller and weighed slightly more than women, but BMI was significantly greater in women. Women had a higher percentage of total body fat compared with men, but men had a greater % trunk fat than women. Finally, women had significantly greater adiponectin levels than men. This sex difference remained significant for every age group and even after adjusting for BMI or the other body fat traits (data not shown).

Table 2 shows the phenotypic correlations among adiponectin and body composition measurements adjusted for age, sex, and height. In the total sample, BMI, percentage of body fat, and especially % trunk fat were inversely associated with serum adiponectin levels. Interestingly, BMI and all body fat traits were significantly negatively associated with adiponectin in women. However, in men, only % trunk fat was strongly negatively associated with adiponectin, whereas the correlation between BMI and adiponectin did not reach statistical significance among women.

Heritability of adiponectin was 33.2% ($P < .01$), and age, sex, and BMI explained 23.4% of adiponectin variability (Table 3). In addition, considering existing sex differences in adiponectin levels, and reported sex-specific genetic effects for fat and fat-free mass [26], we further estimated the heritability for adiponectin by sex (Table 3). These analyses revealed significant heritability of adiponectin among men (heritability, 34%; $P < .05$), but not among women.

4. Discussion

A wide range in the heritability of adiponectin has been reported across ethnically diverse populations [15-19,27,28]. This heterogeneity may have resulted from methodological differences across studies, but also from heterogeneity in the underlying genetic effects and with age. To our knowledge, ours is the first study to estimate genetic and environmental influences on adiponectin in families of African origin living outside the United States. The only existing study in African Americans reported very high heritability for adiponectin levels (82%) in 311 nondiabetic individuals from 21 families, including 1800 relative pairs [18]. This heritability estimate may not apply to other African populations because results in African Americans may be confounded by European admixture. In addition, our study was completed in a homogenous collection of multigenerational families of African heritage, including 3426 relative pairs recruited without regard to their health status. Therefore, our study adds to the evidence for a significant genetic contribution to the variation in adiponectin levels in populations of African descent.

Consistent with results from previous studies of non-African populations [2,27], body fat–related traits were correlated inversely with adiponectin among Afro-Caribbeans. The associations between body fat–related traits and adiponectin were generally stronger in women than in men, but this might also be due to the smaller sample of men. However, both in men and in women, % trunk fat had a similar strong inverse association with adiponectin. It is possible that increases in total body fat may have different effects on adiponectin among women than among men. Moreover, adiponectin progressively decreased with increasing BMI among women but not among men, suggesting that obesity characterized by BMI may have a higher impact on adiponectin levels than in men.

The mean level of adiponectin in men and in women in the present study was similar to the levels of adiponectin in African Americans from at least one study [29], but was higher than in other studies in populations of African origin [12,13]. However, most other past studies have focused on children [11] and young adults [14] of African descent.

We have found significantly higher adiponectin levels in Afro-Caribbean women than in men, even after adjusting for BMI and body fat distribution, which are consistent with the results reported previously by several other studies [2]. Significant sex differences in adiponectin level after adjusting for BMI and other body fat measures were also reported in whites [2], prompting the hypothesis that

sex may have an additional independent effect on adiponectin concentrations [2]. Sex differences in adiponectin levels may not occur in the prepubertal period [30], but develop during the pubertal transition, suggesting that serum androgen or estrogen levels may account for the sex differences seen in adults [31].

The heritability of adiponectin in men was 32% with very little evidence of environmental factors contributing to the variance in adiponectin (5%). In contrast, we found no evidence for heritability of adiponectin in women, whereas environmental factors explained 17% of the total variance in adiponectin. Sex differences in the relative importance of genetic and environmental effects indicate a possible larger familial component for adiponectin levels in men. These differences could also be related to sex differences in body fat distribution and accumulation, interaction with sex chromosomes, or differences arising from sex-specific hormonal factors or other environmental exposures, such as diet. If sex-specific genetic effects are confirmed, then these results may have broader implications for mapping adiponectin regulatory loci because they may suggest that appropriately choosing and subdividing populations by sex and age may be critical for detection of linkage and association with adiponectin levels. Nonetheless, the number of men was relatively small and the power to detect sex differences in heritability was limited and should be confirmed in future studies.

The adiponectin gene is located on chromosome 3q27, where genome-wide scans in humans have mapped a susceptibility locus for type 2 diabetes mellitus and the metabolic syndrome [32,33]. Genetic contribution to the variance in type 2 diabetes mellitus and obesity is very likely to be polygenic, and additionally, these diseases are influenced by multiple environmental factors. On the other hand, fewer genes might be involved in intermediate phenotypes, and the effect of environmental exposure may be less important. Therefore, studies of heredity of intermediate phenotypes, such as adiponectin, may be of great importance when studying the genetics of type 2 diabetes mellitus, obesity, or metabolic syndrome. Our data indicate that serum adiponectin levels are heritable and that genetic factors are a significant source of interindividual differences in circulating adiponectin in Afro-Caribbeans. However, the estimate of total heritability does not provide clues as to how many genetic loci may be contributing to the variation in adiponectin. Our next step will be the identification of the genes that influence adiponectin levels. This may provide important new insight into the pathophysiology of diabetes and obesity among populations of African origin. Our results also raise the possibility that the genetic regulation of serum adiponectin levels may differ by sex among this Afro-Caribbean population. If confirmed, this observation may have practical implications for studies aimed at identifying the loci that control adiponectin concentrations in populations of African heritage.

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