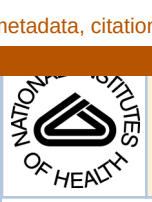

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ADIPOQ, *ADIPOR1*, and *ADIPOR2* Polymorphisms in Relation to Serum Adiponectin Levels and Body Mass Index in Black and White Women

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Abstract

Adiponectin is an adipose-secreted protein with influence on several physiologic pathways including those related to insulin sensitivity, inflammation, and atherogenesis. Adiponectin levels are highly heritable and several single nucleotide polymorphisms (SNPs) in adiponectin-related genes (*ADIPOQ, ADIPOR1*, *ADIPOR2*) have been examined in relation to circulating adiponectin levels and obesity phenotypes, but despite differences in adiponectin levels and obesity prevalence by race, few studies have included black participants. Using cross-sectional interview data and blood samples collected from 990 black and 977 white women enrolled in the Southern Community Cohort Study from 2002 to 2006, we examined 25 SNPs in *ADIPOQ,* 19 in *ADIPOR1*, and 27 in *ADIPOR2* in relation to serum adiponectin levels and body mass index (BMI) using race-stratified linear regression models adjusted for age and percentage African ancestry. SNP rs17366568 in *ADIPOQ* was significantly associated with serum adiponectin levels in white women only (adjusted mean adiponectin levels = 15.9 for G/G genotype, 13.7 for A/G, and 9.3 for A/A, p=0.00036). No other SNPs were associated with adiponectin or BMI among blacks or whites. Because adiponectin levels as well as obesity are highly heritable and vary by race but associations with polymorphisms in the *ADIPOQ, ADIPOR1,* and *ADIPOR2* genes have been few in this and other studies, future work including large populations from diverse racial groups is needed to detect additional genetic variants that influence adiponectin and BMI.

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DISCLOSURE STATEMENT

The authors have no conflicts of interest to declare.

Keywords

Adiponectin; obesity; genetics; African Americans

INTRODUCTION

Adiponectin is a collagen-like protein secreted by adipose tissue and found in relatively high concentration in serum (1). Adiponectin plays an important role in several physiological pathways including those related to insulin action, inflammation, and atherogenesis (1, 2) and is believed to affect the development and progression of several diseases including cardiovascular disease, diabetes, and cancer at several sites including breast, endometrial, and colorectal (3, 4). Adiponectin levels show a strong inverse association with adiposity (1) and also vary by gender and race with lower levels in women compared to men (5) and in blacks compared to whites (6).

Adiponectin is encoded by the gene *ADIPOQ,* located on chromosome 3q27. Two adiponectin receptors have been identified and are encoded by the genes *ADIPOR1* (located on chromosome 1q32) and *ADIPOR2* (located on chromosome 12q13). Heritability estimates for adiponectin are high (ranging from 30% to 70%) (7, 8) indicating that the genes encoding adiponectin and its receptors are plausible candidates for association with serum levels of the protein. Additionally, because adiponectin is strongly associated with body size, the adiponectin-related genes are also reasonable candidate genes for association with obesity phenotypes. Single nucleotide polymorphisms (SNPs) in the *ADIPOQ, ADIPOR1* and *ADIPOR2* genes have been examined in association with adiponectin levels and obesity phenotypes in several studies but results have been quite inconsistent (7). Further, virtually no studies of these genes have included black participants despite known racial differences in the prevalence of obesity (9) and evidence showing differences in adiponectin levels by race (6). Thus, the goal of this study was to examine polymorphisms in *ADIPOQ, ADIPOR1* and *ADIPOR2* in relation to adiponectin levels and body mass index (BMI) in a large sample of both black and white women.

METHODS AND PROCEDURES

Institutional Review Boards at Vanderbilt University, Meharry Medical College, and the University of North Carolina at Chapel Hill approved this study.

Study population

The Southern Community Cohort Study (SCCS) is a prospective epidemiologic cohort study designed to examine racial disparities in cancer incidence and mortality and other health outcomes (10). Study enrollment began in 2002 in twelve southeastern states at Community Health Centers (CHC) which are government-funded facilities providing health services primarily to low-income individuals in medically underserved areas. As described previously (10), participants were required to be age 40–79 years of age, English-speaking, and not have undergone treatment for cancer within the past year. From over 47,000 participants enrolled through early 2006, a sample of 2,000 women who provided a blood sample at study enrollment and self-reported their race as only ‘Black/African American’ or ‘White’ was selected for biomarker analyses. This included a random sample of 395 women selected in 2005 within strata of race (black/white), BMI (18.5–24.9, 25–29.9, and 30–45), and smoking cigarette status (current/former/never), and a second random sample of 1,605 women selected in 2006 in equal numbers across race, BMI (18.5–24.9, 25–29.9, 30–34.9, and 35–45), and menopausal status categories (pre/post).

Data collection

Trained study interviewers conducted structured baseline interviews with participants using a computer-assisted interview which elicited information including demographics, anthropometrics, and several aspects of health and behavior. Height and weight at the time of the baseline interview were self-reported by participants and used to calculate BMI as [weight (kg)]/[height $(m)^2$]. For the 20% of women who were patients in the CHC on the day of the baseline interview, measured height and weight were abstracted from medical records for validation purposes.

A convenience blood sample was collected at the time of recruitment using one EDTA-containing plasma BD Vacutainer® tube and one serum BD Vacutainer® tube. For this study, the median time between the last reported meal and blood collection was 6.0 hours for blacks and 6.3 hours for whites. Fasting blood, defined as at least 8 hours since last meal, was collected for 44% of the participants. Blood samples were shipped cold to Vanderbilt University in Nashville, TN, where they were processed for storage at −80° C. 84% of the blood samples were received the day after the blood draw and 98% were received within two days. The samples were frozen for an average of 2.6 years (range 3 months to 5 years) prior to analysis.

Adiponectin measurement

Adiponectin was measured in serum by immunoassay using the LINCOplex kit (Luminex® xMAP™ Technology, St. Louis, MO) in the Vanderbilt Hormone Assay and Analytical Services Core Laboratory in duplicate for each woman. The average of the two measurements was used in all analyses. Duplicate sets of samples for five randomly selected women as well as five repeat samples from each of two pooled samples were measured to assess the reliability of the assay. Adiponectin was successfully measured in 1,992 of the 2,000 samples (eight samples failed due to a filter plate error or low sample volume). The intra-assay coefficient of variation for the 1,992 samples run in duplicate was 9.4%.

Genotyping of SNPs

SNPs located in the three genes encoding adiponectin and its receptors, *ADIPOQ, ADIPOR1,* and *ADIPOR2*, were selected for this study. The Caucasian (CEU) and West African (YRI) populations in the International HapMap project (release 22) were the primary data source for the selection of the SNPs (11). We identified all HapMap SNPs within each gene including an additional 10 kb to each flank (encompassing potential regulatory elements).. All SNPs were scored for the ability to perform well on the Illumina GoldenGate genotyping platform using an Illumina in-house algorithm (Illumina Inc., San Diego, CA). SNPs that failed the scoring for the Illumina assay were omitted as were those with a minor allele frequency (MAF) < 0.05 in both CEU and YRI subjects while SNPs with a MAF ≥ 0.05 for either CEU or YRI subjects were retained. The LDSelect algorithm was then run separately for the CEU and YRI data using an r^2 cut-off of 0.8 to partition SNPs into LD bins for each population (12). When multiple tagging SNPs were found for a linkage disequilibrium (LD) bin, those SNPs designated as tagging SNPs in both populations were preferentially selected for efficiency. Among equivalent tag SNPs of a given LD bin, one categorized as a candidate functional SNP or one previously employed on Illumina chips was preferentially selected for assay. The total selected set of tagging SNPs efficiently and systematically captured genetic diversity at these genes in both populations. Twenty-five tagging SNPs were selected for the *ADIPOQ* gene, 19 for *ADIPOR1*, and 27 for *ADIPOR2*.

An additional 300 SNPs were selected as ancestry informative markers (AIM) (13). AIMs were required to pass the Illumina scoring algorithm, be at least 5 Mb from the candidate

genes, have a MAF > 0.05 in both the CEU and YRI populations, and have an allele frequency difference between the CEU and YRI populations > 0.6. Of the 300 selected AIM SNPs, 292 passed the Illumina scoring algorithm and 276 were successfully genotyped.

Genomic DNA was extracted from buffy coat using QIAamp DNA kits (Qiagen, Valencia, CA) according to manufacturers' instructions. Genotyping took place at Vanderbilt University. The SNPs included in this project were genotyped along with those from a larger study of obesity in this study population to facilitate the use of the Illumina GoldenGate genotyping platform (Illumina Inc., San Diego, CA). Blinded QC samples (N=29) and another 171 pairs of duplicated samples were included and the consistency rate was 99.9%.

Statistical Methods

Of the 2,000 women selected for analysis, genotyping was successful for 1,990. Individuals were assigned admixture estimates (called ancestry allelic clusters or AAC) using the 276 genotyped AIMs and STRUCTURE Version 2.2.3 software (14). Given that the participants in this project were selected for inclusion based on self-reported race being only black or white (and the number of Asian and Hispanic participants in the SCCS overall is very low), the number of ancestral populations to be estimated was *a priori* specified to be 2. Thus two AACs were generated for each individual: one for African ancestry and one for European ancestry. Twenty-three women were excluded from further analysis because of discrepancies between self-reported race and ancestry estimates derived from STRUCTURE (6 self-reported black women with less than 20% estimated African ancestry and 17 self-reported white women with more than 30% estimated African ancestry) leaving 1,967 women for study (N=990 black and N=977 white). For analyses with adiponectin as the primary outcome, data from 1,959 women were analyzed after excluding eight additional samples in which adiponectin could not be measured due to low blood sample volume or a filter plate error.

We tested for Hardy-Weinberg equilibrium in race-stratified samples and found one SNP in *ADIPOQ* (rs1648707) that showed significant deviation from Hardy-Weinberg equilibrium in both white ($p=8.6\times10^{-16}$) and black ($p=1.3\times10^{-16}$) women. This SNP was excluded from all further analyses.

Linkage disequilibrium (LD) was calculated and displayed between each of the genotyped SNPs, stratified by race, using the r^2 metric and Haploview software (Supplementary Figure 1).

Associations between individual SNPs and adiponectin levels were examined using race-stratified multiple linear regression models with log-transformed adiponectin as the outcome (adjusted mean adiponectin levels for each genotype were back-transformed for presentation). Similar models were also constructed with BMI as the outcome variable. SNPs that were found to have a MAF < 0.001 within a race group were omitted from further analyses in that race group. SNPs were generally examined using a codominant inheritance model (with 2 degrees of freedom) which was selected because there was no *a priori* hypothesis about the model form for the SNP-adiponectin associations or the SNP-BMI associations, and the use of the two degree of freedom test for the co-dominant model has been shown have good overall performance for any of the possible underlying modes of inheritance (15). The referent genotype was selected to be the most common race-specific homozygous genotype. For SNPs in which less than 10 women had the rare homozygous genotype, a dominant model was used that combined women with the rare homozygous genotype with those with the heterozygous genotype. Each regression model included adjustment for age at baseline SCCS interview as well as percentage of African ancestry as estimated by STRUCTURE. Models substituting the first five principal components derived

using EIGENSTRAT software (16) in place of the AAC derived from STRUCTURE were also examined and found to have very similar results. SAS/STAT version 9.2 (SAS Institute, Cary, NC) was used for all modeling.

A Bonferroni correction was applied to the *a priori* alpha level of 0.05 and was calculated based on the number of individual models examined for each SNP over the three genes of interest. p-values of 0.00096 and 0.00075 were used to determine statistical significance for white and black women, respectively, based on the analysis of 52 and 67 SNPs.

RESULTS

Consistent with the stratified sampling design for this study, equal percentages of black and white women were post-menopausal, and women in both race groups had a mean BMI (BMI) of approximately 30 kg/m^2 (Table 1). Income and education distributions between the race groups were also similar. Adiponectin levels were lower in black women than in white women (15.4 v 19.9, mg/ml, p<0.0001). There were no differences in adiponectin levels by fasting blood status (black fasting v. non-fasting mean=14.9 v. 15.9, p=0.25; white fasting v. non-fasting mean=20.2 v. 19.6, p=0.6).

The location and genotype frequencies of the SNPs selected for the three genes of interest are described in Tables 2a, 2b, and 2c. Genotyping was successful for all 1,967 women for 58 (84%) of the SNPs and over 96% complete for the other 11 SNPs. More tag-SNPs were needed to provide adequate gene coverage for the black sample compared to the white sample.

Adjusted mean adiponectin levels by genotype are shown in Figure 1 for *ADIPOQ, ADIPOR1*, and *ADIPOR2* separately for black and white women. Among white women, one SNP, rs17366568 in the *ADIPOQ* gene, met the Bonferroni p-value threshold for significance. The adjusted mean adiponectin levels for rs17366568 were 15.9 for white women with the G/G genotype, 13.7 for those with the A/G genotype, and 9.3 for those with the A/A genotype (p=0.00036). This SNP was not in LD with any of the other genotyped SNPs (Supplementary Figure 1). The additive genetic model was also examined for SNP rs17366568 in *ADIPOQ* in white women, and this SNP was significantly associated with adiponectin using the additive model with little difference seen compared to the co-dominant model (additive model p-value=0.0002). BMI was added as a covariate to the linear regression model for rs17366568 in *ADIPOQ* in relation to adiponectin levels, and while BMI was found to be strongly associated with adiponectin itself, its inclusion did not alter the association between the SNP and adiponectin levels in white women (mean adiponectin levels for rs17366568 were 15.9 (G/G genotype), 13.6 (A/G), and 9.7 (A/A), p=0.00011 after adjustment for BMI).

The genotype distribution for SNP rs17366568 differed significantly between the white and black women (χ^2 p-value <0.0001). For the black women, adjusted mean adiponectin levels were 11.7 for women with the G/G genotype and 11.6 for women with the A/G or A/A genotypes (only one black woman had the A/A genotype) and the SNP was not associated with adiponectin levels using a dominant genetic model (p=0.92).

Interactions between SNP rs17366568 and BMI, diabetes status, and menopausal status in white were also examined. Of these factors, only BMI was found to be a significant effect modifier of the SNP-adiponectin association (likelihood ratio p-value < 0.0001 for interaction). A strong positive association was seen for adiponectin levels among non-overweight women (<25 kg/m^2) (adiponectin=8.1, 19.3, and 23.7 ug/ml for A/A, A/G, and G/G genotypes, respectively; p=0.004); this marked increase in adiponectin levels across genotype was not as clear in the other strata of BMI (25–29.9, 30–34.9, and 35–45 kg/m^2).

However, these interaction models should be considered exploratory as the number of individuals in some cells was very small (for example, N=3 for individuals with BMI <25 kg/m^2 and genotype A/A).

Beyond SNP rs17366568 in white women, we observed no significant associations between adiponectin levels and individual SNPs in either the black or white women. Figure 2 shows adjusted mean BMI values by genotype for the three genes of interest. There was little variation by BMI across genotypes in any of the SNPs and none met the Bonferroni p-value thresholds for significance although p-values less than 0.05 were observed for five SNPs in *ADIPOR2* among the black women.

DISCUSSION

This study examined variation in three adiponectin-related genes in relation to adiponectin levels and BMI in a large sample of black and white women. We observed a significant association between adiponectin levels and SNP rs17366568 in *ADIPOQ* among white women but this SNP was not found to be associated with adiponectin levels among black women. Determining SNPs that affect either adiponectin levels or BMI, and ascertaining whether these SNPs differ across racial groups, is an important step in our understanding of the roles played by adiponectin and obesity in the complex mechanisms underlying racial disparities for major chronic disease such as cancer, diabetes, and cardiovascular disease.

Individuals of African descent display, on average, more variation in allele frequency than do people of European descent, indicating that the frequency of etiologically important SNPs may differ by race. The difference in the association with adiponectin levels and SNP rs17366568 between black and white women in this study seems at least in part due to allele frequency differences, with a MAF (A allele) of 0.14 in the white women and only 0.015 in the black women. This is consistent with the results of the HapMap project in which all of the YRI samples were found to have the G/G genotype (and thus this SNP is not shown on the LD plot for the HapMap YRI population, Supplementary Figure 2, top panel).

The statistically significant results for SNP rs17366568 in *ADIPOQ* in white women in relation to adiponectin from our study were very similar to those seen in two recent genome-wide association studies (GWAS) studies of European whites (8, 17). The A/A genotype was relatively rare in our study (MAF=0.14 in white women) as it was in the two GWAS (MAF=0.11 and 0.13) (8, 17). The effect size (using log-transformed adiponectin, ug/ml, as the outcome) for an additive model was 0.20 for each addition of the G allele in the KORA portion of the Heid study (8), which was very close to our effect estimate of 0.18 for a similar model. The proportion of variance explained by this SNP was 1.7% in our study, lower than the 5.3% reported for women in one GWAS (8) but close to the <2% reported in the other GWAS (17). These similar findings are especially striking given the difference in study design between the GWAS and our biological hypothesis-driven study. A third GWAS conducted in white Europeans reported four SNPs in *ADIPOQ* to be significant associated with circulating adiponectin, one of which was measured in our study (rs6444175) and found not to be associated with adiponectin in whites (p=0.5), another (rs1648707) which was in strong LD with a SNP genotyped in our study (rs182052) which was also not associated with adiponectin in whites (p=0.1), and two not genotyped in our study (18).

In our study, we found no additional SNPs beyond rs17366568 that were associated with adiponectin in black or white women. Adiponectin levels have been examined in relation to variants in *ADIPOQ* in more than a dozen association studies of white and Asian individuals but few specific SNPs or haplotypes have been replicated in multiple populations. Four common *ADIPOQ* polymorphisms (rs2241766 (commonly called 45T→G), rs1501299

(commonly called 276G→T), −11391G→A, and −11377C→G) were genotyped in early candidate gene studies for association with adiponectin with inconsistent results (19–27). Several of these studies were examined in a 2007 meta-analysis of genetic variants in *ADIPOQ* in relation to adiponectin levels. Menzaghi et al. reported that two commonly typed SNPs in *ADIPOQ*, rs17300539 and rs1501299, were significantly associated with adiponectin levels in the meta-analysis of five and twelve studies, respectively (7). Neither of these SNPs was genotyped in our study but each was in strong LD with selected tag-SNPs that were genotyped. In the HapMAP CEU population (release 22), both rs822387 and rs16861210 had a pairwise r^2 value of 0.82 with rs17300539, but neither was found to be significantly associated with adiponectin levels in white women in our study (p=0.2 for rs822387 and p=0.1 for rs16861210). SNP rs6444175 in *ADIPOQ* had a pairwise r^2 value of 0.92 in the CEU population and an r^2 of 0.53 in the YRI population with rs1501299, but rs6444175 was not significantly associated with adiponectin levels in our study (p=0.5 for white women and p=0.6 for black women). As genotyping larger numbers of SNPs has become easier and more cost-efficient, additional SNPs in *ADIPOQ* have been examined in relation to adiponectin levels but still little consistency has been observed in association with adiponectin across studies (5, 28–31).

LD plots for *ADIPOQ* for the HapMap YRI and CEU populations are shown in Supplementary Figure 2 (top and bottom panels, respectively) and the differences in the LD structures between the YRI and CEU populations demonstrate the importance of examining genetic correlates of adiponectin and obesity in racially diverse populations. However, to date, polymorphisms in *ADIPOQ* have been examined largely in populations that did not include individuals of African descent. One genome-wide linkage scan which included both 89 Hispanic families and 42 black families reported heritability estimates of 71% and 64% in Hispanics and blacks, respectively, for adiponectin, but the region of the genome where *ADIPOQ* is located was identified as a major quantitative trait loci only in the Hispanic sample (32). The HERITAGE study included 276 black participants and found two variants in *ADIPOQ* that were associated with measures of body fat in blacks but not whites (33). In a recent study from the CARDIA population, ten tagSNPs were examined and five were found to be significantly associated with adiponectin among white participants while only one SNP was found to be marginally significant among blacks (34). Comparisons to our results are limited by the combination of effects across gender groups, the narrower age range of participants (33–45 years), and the genotyping of a different set of tagSNPs in the CARDIA study. Collectively, the body of literature examining genetic variation in adiponectin-related genes among blacks is small, but studies to date, including ours, offer an indication that different variants may have differing effects on circulating levels across race groups.

Regarding BMI, several studies have reported positive associations between BMI and a variety of *ADIPOQ* polymorphisms (35–38) while others have not found any significant effects (20, 23, 27, 30, 33). No significant associations with BMI were found with SNPs in *ADIPOQ* in the Menzaghi et al. 2007 meta-analysis (7). Of the SNPs in *ADIPOQ* examined to date in relation to BMI, only rs182052, found to be associated with BMI in a group of over 800 Hispanic individuals (37), was also genotyped in our study but we did not find any association with BMI in black (p=0.95) or white women (p=0.14).

Very few studies have examined polymorphisms in *ADIPOR1* and *ADIPOR2* in relation to adiponectin or BMI. No genome-wide significant associations between adiponectin levels and SNPs in either *ADIPOR1* or *ADIPOR2* were found in a GWAS of Europeans (17). Loos et al. investigated two SNPs in *ADIPOR1* (rs1539355 and rs2275737) and two in *ADIPOR2* (rs0773982 and rs2058112) in relation to BMI in French-Canadians and found no

statistically significant associations (27); we also observed no association with BMI for these four SNPs in black or white women.

High heritability estimates for both adiponectin levels and obesity as well as linkage studies showing the adiponectin-related genes to be strongly related to these phenotypes indicate that, while the evidence to date has been inconsistent, polymorphisms in the genes encoding adiponectin and the two known adiponectin receptors remain promising avenues for explaining variation in adiponectin levels as well as obesity. Conflicting results to date may be due to a myriad of differences across studies including sample size, analysis methodology (including the examination of single-SNPs versus haplotypes, differing approaches to confounding, control for population stratification, and multiple comparisons), genetic background, and possibly environmental or gene-gene influences across populations.

It remains possible that there are unknown rare variants that have a strong effect on adiponectin levels, and few studies to date, including ours, have been powered to detect rare variants. There may also be many as-yet unidentified common loci with small individual effects on adiponectin levels. Additionally, genetic contribution to adiponectin variation may be influenced by interactions between multiple loci or between loci and environmental factors or perhaps by epigenetic factors, none of which have been carefully examined yet.

A major strength of this study was the use of participants from the SCCS which allowed for the examination of adiponectin levels and BMI in relation to genetic variation in adiponectin-related genes in both black and white women of similar socioeconomic status and geographic locale. SNPs were selected to provide coverage across the genes using both the HapMap CEU and YRI populations which resulted in similar precision in estimating sequence variation in both the black and white participants. The large sample of black and white women provided adequate power to detect meaningful changes in adiponectin and BMI. Power calculations for adiponectin show that for changes in adiponectin levels greater than 5.0 ug/mL across genotypes, SNPs with MAF greater than 0.07 were well-powered (power ≥ 80%). For BMI, power was above 80% for all but the SNPs with the lowest MAF (<0.06) for a change in BMI of 2.5 kg/m^2 across genotypes.

Study limitations include the potential for measurement error in either of the outcome variables of adiponectin and BMI. As is common in large population-based studies, we measured total adiponectin rather than high-molecular weight adiponectin. Additionally, we only measured adiponectin at one point in time; however, adiponectin levels measured one year apart have been reported to be highly correlated and likely sufficient for large epidemiologic studies (39). We also did not require participants to provide fasting blood samples although we found no differences in the mean adiponectin levels by fasting status. For BMI, we used self-reported height and weight measures to calculate BMI. While there is evidence to indicate that women tend to over-report height while under-reporting weight (40), BMI values calculated from self-reported height and weight in the SCCS were very highly correlated with BMI values calculated from medical record data overall (Pearson correlation coefficient > 0.95) as well as across strata of race and BMI, indicating that the self-reported values are generally of high quality. A further limitation of this study is the lack of information regarding central obesity, which may be a stronger correlate of disease risk than BMI and has been observed to vary across race groups for a given BMI (41). Finally, the use of a Bonferroni correction is a potential limitation as it is a conservative approach that is unable to account for the correlation structure inherent among a group of SNPs (42). Despite the conservative nature of the Bonferroni correction, its application did not drastically alter the interpretation of these results. There were few SNPs that were significantly associated with adiponectin or BMI at an alpha level of 0.05 (5 total for adiponectin and 9 total for BMI, out of 119 total associations examined). Further, there was

no evidence of clustering of SNPs with lower p-values in any specific regions of the genes examined. None of these 14 SNPs are known to be functional variants nor have they been found in previous studies to be associated with these outcomes. They may, however, represent areas of the genes worthy of further exploration in future studies.

In this study of genetic variation in adiponectin-related genes in relation to adiponectin and BMI among both black and white women, we demonstrated that there may be different genetic variants that contribute to variation in adiponectin levels by race. Our observation of an association between SNP rs17366568 in *ADIPOQ* and adiponectin levels in white women was also recently reported by two GWAS of European women. To our knowledge, our study is the first to examine these three genes in relation to adiponectin among black women and we did not find any association with SNP rs17366568 or others in black women. Additionally, we found no other SNPs that were associated with adiponectin levels or with BMI in black or white women. Future discovery of additional variants that affect adiponectin levels (and particularly rare variants that may occur only in certain race groups) as well as detection of gene-gene and gene-environment interactions related to adiponectin levels and BMI will require future studies with large sample sizes from multiple racial groups.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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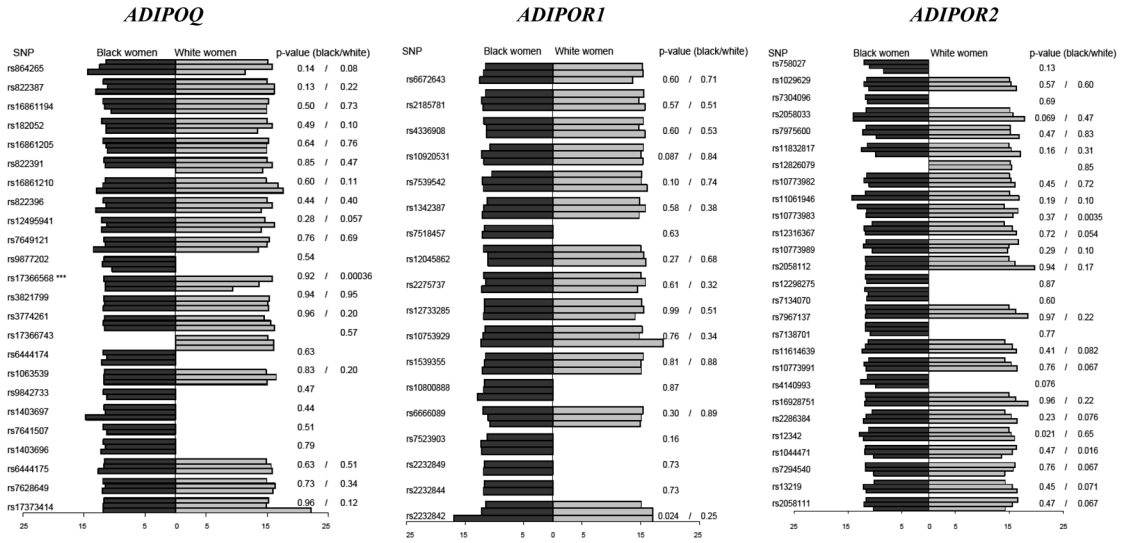

Figure 1.

Adjusted mean adiponectin levels (ug/ml) and associated p-values from race-stratified linear regression models for SNPs in *ADIPOQ* (left panel), *ADIPOR1* (center panel), and *ADIPOR2* (right panel) among 990 black women and 977 white women, Southern Community Cohort Study, 2002–2006. The horizontal bars represent mean adiponectin levels for each SNP by genotype with the top bar in each grouping representing the Test/Test genotype, the middle bar representing the Test/Reference genotype, and the lower bar representing the Reference/Reference genotype (see Tables 2a, 2b, and 2c for Test and Reference allele listings). Two bars indicate that the rare homozygous genotype was combined with the heterozygote genotype for analysis. p-values refer to tests for differences in adiponectin levels across genotypes. SNP meeting the Bonferroni p-value threshold indicated by asterisks (***).

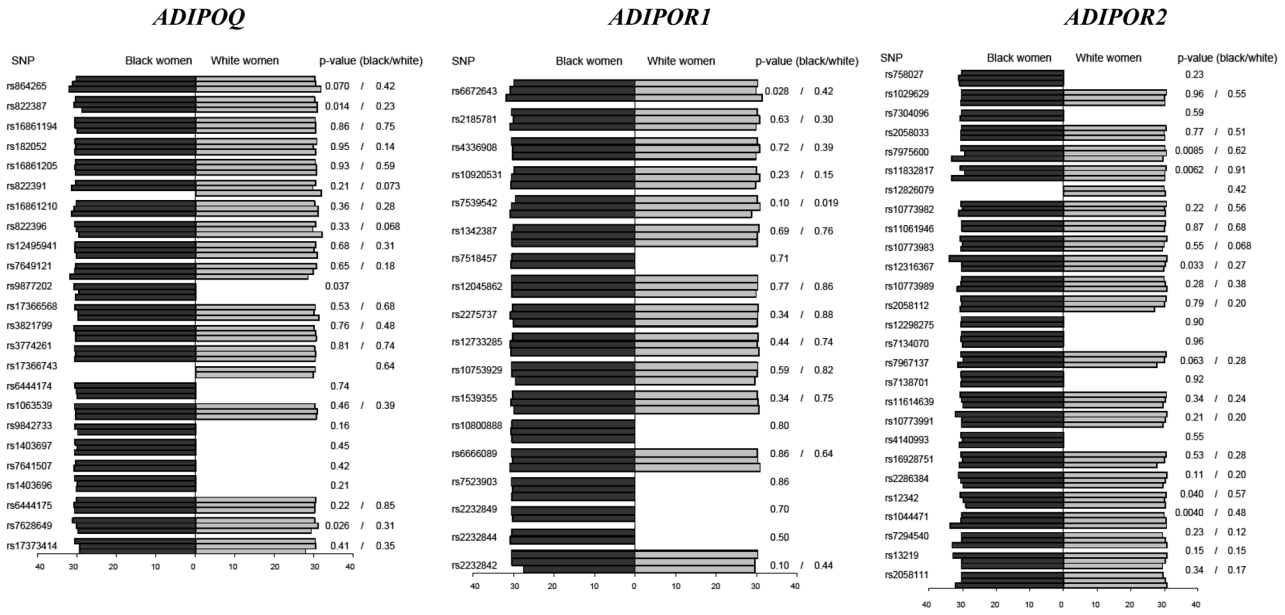

Figure 2.

Adjusted mean body mass index (BMI) (kg/m^2) values and associated p-values from race-stratified linear regression models for SNPs in *ADIPOQ* (left panel), *ADIPOR1* (center panel), and *ADIPOR2* (right panel) among 990 black women and 977 white women, Southern Community Cohort Study, 2002–2006. The horizontal bars represent mean adiponectin levels for each SNP by genotype with the top bar in each grouping representing the Test/Test genotype, the middle bar representing the Test/Reference genotype, and the lower bar representing the Reference/Reference genotype (see Tables 2a, 2b, and 2c for Test and Reference allele listings). Two bars indicate that the rare homozygous genotype was combined with the heterozygote genotype for analysis. p-values refer to tests for differences in BMI across genotypes.

Table 1

Characteristics of black and white women genotyped for *ADIPOQ, ADIPOR1,* and *ADIPOR2* from the Southern Community Cohort Study, 2002–2006

	Black women (N=996)		White women (N=994)	
	Mean	**[std]**	**Mean**	**[std]**
Age at baseline interview (years)	50.1	[8.9]	49.9	[8.6]
Body mass index (kg/m^2)	30.4	[6.4]	30.3	[6.6]
Adiponectin (ug/ml)	15.4	[13.4]	19.9	[16.1]
	N (%)		**N (%)**	
Education				
<9 years	78 (7.8)		86 (8.7)	
9–11 years	243 (24.4)		221 (22.2)	
Completed high school	411 (41.3)		411 (41.4)	
More than high school	264 (26.5)		276 (27.8)	
Annual Household Income				
< $15,000	621 (62.9)		597 (60.3)	
$15,000 – 24,999	233 (23.6)		199 (20.1)	
$25,000 – 49,999	116 (11.8)		130 (13.1)	
$50,000+	17 (1.7)		64 (6.5)	
Missing	9		4	
Menopausal status				
Pre	497 (49.9)		497 (50.0)	
Post	499 (50.1)		497 (50.0)	
Diabetes[a]				
Yes	218 (21.9)		162 (16.3)	
No	778 (78.1)		832 (83.7)	

[a]Self-reported from the question “Has a doctor ever told you that you have had diabetes?”

Table 2a

Characteristics of *ADIPOQ* SNPs genotyped in black and white women in the Southern Community Cohort Study

						Genotype frequency					
						Black women (N=990)			White women (N=977)		
SNP	**Gene region**	**Tagging population**	**Test allele**	**Reference allele**	**N**	**T/T**	**T/R**	**R/R**	**T/T**	**T/R**	**R/R**
rs864265	5′ near gene	YRI, CEU	C	A	1,967	0.75	0.23	0.02	0.70	0.27	0.03
rs822387	5′ near gene	YRI	A	G	1,967	0.45	0.44	0.11	0.83	0.16	0.008
rs16861194	5′ near gene	YRI, CEU	A	G	1,967	0.57	0.38	0.05	0.84	0.16	0.006
rs182052	5′ near gene	YRI	G	A	1,967	0.41	0.48	0.11	0.44	0.44	0.12
rs16861205	5′ near gene	YRI	G	A	1,967	0.64	0.33	0.04	0.85	0.14	0.006
rs822391	Intron 1	CEU	A	G	1,967	0.92	0.08	0	0.62	0.32	0.06
rs16861210	Intron 1	YRI, CEU	G	A	1,967	0.68	0.29	0.03	0.82	0.17	0.01
rs822396	Intron 1	CEU	A	G	1,967	0.63	0.32	0.05	0.65	0.31	0.05
rs12495941	Intron 1	YRI, CEU	C	A	1,967	0.40	0.46	0.14	0.43	0.46	0.11
rs7649121	Intron 1	CEU	A	T	1,967	0.79	0.20	0.01	0.68	0.29	0.02
rs9877202	Intron 1	YRI	A	G	1,967	0.71	0.26	0.03	0.99	0.002	0
rs17366568	Intron 1	CEU	G	A	1,967	0.97	0.03	0.001	0.75	0.23	0.02
rs3821799	Intron 1	CEU	G	A	1,967	0.18	0.49	0.33	0.33	0.47	0.20
rs3774261	Intron 1	YRI, CEU	G	A	1,967	0.18	0.50	0.31	0.41	0.45	0.15
rs17366743	Intron 2	CEU	A	G	1,967	0.99	0.01	0	0.95	0.05	0.003
rs6444174	Intron 2	YRI	A	G	1,963	0.70	0.27	0.03	0.99	0.006	0
rs1063539	Exon 3	CEU	C	G	1,879	0.62	0.38	0.002	0.75	0.23	0.02
rs9842733	3′ UTR	YRI	T	A	1,967	0.83	0.16	0.008	0.99	0.003	0
rs1403697	3′ UTR	YRI	A	G	1,967	0.77	0.22	0.02	0.99	0.003	0
rs7641507	3′ near gene	YRI	G	A	1,967	0.85	0.15	0.005	0.99	0.004	0
rs1403696	3′ near gene	YRI	G	A	1,967	0.62	0.33	0.05	0.99	0.007	0
rs6444175	3′ near gene	YRI, CEU	G	A	1,967	0.46	0.46	0.08	0.56	0.36	0.08
rs7628649	3′ near gene	YRI, CEU	G	A	1,967	0.43	0.46	0.11	0.79	0.19	0.01
rs17373414	3′ near gene	CEU	G	A	1,967	0.98	0.02	0.001	0.78	0.20	0.02

Table 2b

Characteristics of *ADIPOR1* SNPs genotyped in black and white women in the Southern Community Cohort Study

						Genotype frequency					
						Black women (N=990)			White women (N=977)		
SNP	**Gene region**	**Tagging population**	**Test allele**	**Reference allele**	**N**	**T/T**	**T/R**	**R/R**	**T/T**	**T/R**	**R/R**
rs6672643	5′ near gene	YRI, CEU	A	G	1965	0.56	0.37	0.07	0.75	0.22	0.03
rs2185781	5′ near gene	YRI, CEU	G	A	1967	0.66	0.30	0.04	0.65	0.30	0.04
rs4336908	5′ near gene	YRI	G	A	1967	0.86	0.13	0.008	0.65	0.30	0.04
rs10920531	5′ near gene	YRI, CEU	C	A	1967	0.24	0.46	0.30	0.43	0.42	0.15
rs7539542	Exon 8	CEU	G	C	1967	0.16	0.44	0.40	0.49	0.40	0.10
rs1342387	Intron 4	YRI	G	A	1966	0.25	0.49	0.26	0.32	0.45	0.23
rs7518457	Intron 4	YRI	A	G	1967	0.88	0.11	0.005	0.99	0.004	0
rs12045862	Intron 3	YRI, CEU	G	A	1967	0.83	0.16	0.009	0.55	0.38	0.07
rs2275737	Intron 1	YRI, CEU	C	A	1967	0.31	0.49	0.20	0.35	0.44	0.21
rs12733285	Intron 1	CEU	G	A	1967	0.62	0.33	0.05	0.49	0.41	0.09
rs10753929	Intron 1	YRI, CEU	G	A	1967	0.65	0.31	0.04	0.76	0.21	0.02
rs1539355	Intron 1	YRI, CEU	A	G	1967	0.29	0.50	0.21	0.49	0.41	0.10
rs10800888	3′ Near gene	YRI	G	A	1967	0.76	0.23	0.01	0.99	0.002	0
rs6666089	3′ Near gene	YRI	G	A	1967	0.75	0.23	0.02	0.49	0.41	0.10
rs7523903	3′ Near gene	YRI	G	C	1963	0.59	0.40	0.01	0.98	0.02	0
rs2232849	3′′ Near gene	YRI	G	A	1967	0.83	0.16	0.009	0.99	0.004	0
rs2232844	3′ Near gene	YRI	A	G	1967	0.83	0.16	0.009	1.00	0	0
rs2232842	3′ Near gene	YRI	A	G	1967	0.71	0.27	0.02	0.94	0.05	0.002

Table 2c

Characteristics of *ADIPOR2* SNPs genotyped in black and white women in the Southern Community Cohort Study

						Genotype frequency					
						Black women (N=990)			White women (N=977)		
SNP	**Gene region**	**Tagging population**	**Test allele**	**Reference allele**	**N**	**T/T**	**T/R**	**R/R**	**T/T**	**T/R**	**R/R**
rs758027	5′ near gene	YRI	A	G	1966	0.81	0.18	0.01	0.99	0.001	0
rs1029629	5′ near gene	YRI	A	C	1966	0.56	0.39	0.05	0.50	0.40	0.09
rs7304096	Intron 1	TRI	A	G	1967	0.93	0.07	0.001	0.99	0.001	0
rs2058033	Intron 1	CEU	A	C	1967	0.95	0.05	0.001	0.76	0.21	0.02
rs7975600	Intron 1	YRI, CEU	T	A	1967	0.75	0.23	0.01	0.73	0.24	0.02
rs11832817	Intron 1	CEU	G	A	1967	0.70	0.28	0.02	0.52	0.40	0.08
rs12826079	Intron 1	CEU	G	A	1966	0.98	0.02	0	0.87	0.12	0.006
rs10773982	Intron 1	YRI, CEU	A	G	1967	0.39	0.47	0.14	0.46	0.43	0.11
rs11061946	Intron 1	CEU	G	A	1966	0.98	0.02	0.001	0.86	0.13	0.004
rs10773983	Intron 1	CEU	G	A	1966	0.07	0.38	0.56	0.49	0.40	0.11
rs12316367	Intron 1	YRI	A	G	1967	0.02	0.26	0.72	0.29	0.49	0.22
rs10773989	Intron 1	YRI	A	G	1967	0.54	0.40	0.06	0.24	0.52	0.25
rs2058112	Intron 1	CEU	G	A	1967	0.62	0.33	0.05	0.75	0.24	0.01
rs12298275	Exon 2	YRI	A	G	1967	0.92	0.08	0.001	1.00	0	0
rs7134070	Intron 2	YRI	A	G	1967	0.74	0.24	0.02	0.99	0.01	0
rs7967137	Intron 2	YRI	A	G	1967	0.51	0.41	0.09	0.75	0.24	0.01
rs7138701	Intron 2	YRI	G	A	1967	0.66	0.31	0.04	0.99	0.01	0
rs11614639	Intron 3	YRI	A	C	1967	0.30	0.51	0.19	0.32	0.49	0.20
rs10773991	Intron 3	YRI	A	G	1967	0.03	0.33	0.64	0.29	0.49	0.22
rs4140993	Intron 4	YRI	A	C	1967	0.70	0.27	0.03	0.99	0.009	0
rs16928751	Exon 6	YRI, CEU	G	A	1967	0.61	0.35	0.05	0.75	0.24	0.01
rs2286384	Intron 6	YRI, CEU	C	G	1967	0.08	0.46	0.46	0.29	0.49	0.22
rs12342	3′ UTR	YRI	G	A	1967	0.65	0.32	0.03	0.49	0.41	0.10
rs1044471	3′ UTR	YRI, CEU	G	A	1967	0.63	0.33	0.04	0.26	0.51	0.23
rs7294540	3′ Near gene	YRI	A	C	1967	0.74	0.25	0.02	0.18	0.49	0.34
rs13219	3′ Near gene	YRI, CEU	A	G	1967	0.02	0.27	0.71	0.33	0.48	0.19

						Genotype frequency					
						Black women (N=990)			White women (N=977)		
SNP	**Gene region**	**Tagging population**	**Test allele**	**Reference allele**	**N**	**T/T**	**T/R**	**R/R**	**T/T**	**T/R**	**R/R**
rs2058111	3′ Near gene	YRI	A	C	1963	0.65	0.32	0.03	0.19	0.48	0.34

UTR = untranslated region

YRI = Yoruban population from HapMap; CEU = Caucasian population from HapMap

T/T = Test/test genotype; T/R = Test/reference genotype; R/R = reference/reference genotype