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Genetic Variation in Adiponectin (*ADIPOQ*) and the Type-1 Receptor (*ADIPOR1*), Obesity and Prostate Cancer in African Americans

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Abstract

Background—Adiponectin is a protein derived from adipose tissue suspected to play an important role in prostate carcinogenesis. Variants in the adiponectin gene (*ADIPOQ*) and its type I receptor (*ADIPOR1*) have been recently linked to risk of both breast and colorectal cancer. Therefore, we set out to examine the relationship between polymorphisms in these genes, obesity and prostate cancer in study of African American men.

Methods—Ten single nucleotide polymorphisms (SNPs) in *ADIPOQ* and *ADIPOR1* were genotyped in DNA samples from 131 African American prostate cancer cases and 344 controls participating in the Flint Men's Health Study. Logistic regression was then used to estimate their association with prostate cancer and obesity.

Results—While no significant associations were detected between any of the tested SNPs and prostate cancer, the rs1501299 SNP in *ADIPOQ* was significantly associated with body mass (p=0.03).

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Conclusions—Genetic variation in *ADIPOQ* and *ADIPOR1* did not predict risk of prostate cancer in this study of African American men. However, the rs1501299 SNP in *ADIPOQ* was associated with obesity. Further investigation is warranted to determine if racial differences exist in the influence of the adiponectin pathway on prostate cancer risk.

Keywords

adipokines; body mass index; genetic susceptibility; single nucleotide polymorphism; racial differences

Introduction

Obese men diagnosed with prostate cancer have been shown to possess more aggressive tumor characteristics, an increased risk for biochemical recurrence and death(1-3). While the mechanism remains unclear, the poorer prognosis observed among obese patients suggests an etiologic heterogeneity driven by androgens, insulin resistance and/or chronic inflammation(4). However, alternative explanations include delayed detection of disease due to false negative prostate specific antigen (PSA) test results(5;6). It has been suggested that PSA hemodilution is the underlying cause of the observed inverse relationship between body mass and PSA concentration(7).

Adiponectin, one of a number of cytokines produced almost exclusively by adipocytes, has been hypothesized as a link between obesity and advanced prostate cancer. An inverse relationship between serum adiponectin concentrations and prostate cancer risk has been demonstrated in a number of studies(8-10), however no study to our knowledge has been able to recruit an adequate number of African Americans to explore the role of adipokines and prostate cancer in this high-risk group of men.

It has been estimated that a significant proportion (30% to 70%) of the variability in circulating plasma adiponectin is influenced by genetics(11). Several variants of the adiponectin (*ADIPOQ*)(12) and receptor 1 (*ADIPOR1*)(13) genes have been associated with obesity(14;15) cardiovascular disease(16), diabetes(14;17) and more recently cancers of the breast and colorectum (18;19). And again, a vast majority of these studies have been conducted in either largely or exclusively Caucasian populations. The relationship between these genes and prostate cancer has not been adequately explored. Therefore, we aimed to examine the association between several variants in *ADIPOQ* and *ADIPOR1* with both obesity and prostate cancer risk using samples collected from an established case-control study of prostate cancer in African American men.

Materials and Methods

The Flint Men's Health Study (FMHS) is a community-based study of prostate cancer in African-Americans between the ages of 40-79. In 1996, 730 men were recruited to participate in the study from a probability sample residing in the city of Flint, Michigan and surrounding communities. Subjects completed a detailed in-home interview, and 379 of these men also participated in a clinical and urologic examination which included measurement of serum PSA. Men with an elevated total PSA (≥4.0 ng/mL) or an abnormal

digital rectal exam were referred for prostate biopsy. Twenty-eight subjects were diagnosed with prostate cancer as a consequence of the initial protocol or during follow-up, resulting in a final sample of 351 controls. A sufficient DNA sample was available for genotyping on 344 of remaining controls.

Prostate cancer cases aged 40 to 79 years and diagnosed between January 1, 1995 and December 31, 2002 were recruited from the same community through the Genesee County Community-Wide Hospital Oncology Program (CHOP) registry. All cases completed a detailed epidemiologic interview and provided a blood sample for DNA analysis. Medical records were reviewed to collect clinical and pathologic stage, Gleason grade, pre-diagnostic PSA and primary treatment. A total of 136 cases were ultimately recruited to participate in the study, with DNA available on 131 for this investigation. Height and weight were measured by trained health professionals. Informed consent was obtained from all study participants and the research protocol has been approved by the Institutional Review Board of the University of Michigan. For both cases and controls, genomic DNA was isolated from whole blood using the Puregene DNA Purification Kit (Gentra Systems, Minneapolis, MN).

SNP Selection and Genotyping Methods

Ten single nucleotide polymorphisms in *ADIPOQ* and *ADIPOR1* were selected in an effort to compare results in this investigation with the findings in breast and colorectal cancer *(ADIPOQ)* -11365 C>G (rs266729), -4034 A>C (rs822395), -3964 A>G (rs822396), +45 T>G (rs2241766), +276 G>T (rs1501299), *(ADIPOR1)* -11760 G>A (rs2232853), -1742 C>T (rs12733285), +5843 C>T (rs1342387), +10225 G>C (rs7539542), +11363 A>C (rs10920531). The SNPs were originally selected based their ability to tag the major haplotype blocks in each gene among samples in their study, a minor allele frequency of greater than 10%, with preferential selection given to SNPs with functional relevance(18;19).

Genotyping for all SNPs was performed using TaqMan SNP Genotyping Assays (Applied Biosystems, Foster City, CA). Genotyping reactions include 2.5 μL of TaqMan master mix, 0.25 μL of Assay SNP Genotyping Assay pre-mix of primers and probes, and 2.25 μL of 5 ng/μL template DNA. All PCR was conducted in a 384-well plate format and subjected to a universal PCR protocol of 95°C for 10 minutes, followed by 40 cycles of denaturation at 92°C for 15 seconds followed by an annealing extension step of 60°C for 1 minute. Reactions were analyzed using the ABI PRISM 7900 HT Sequence Detection System and the SDS Version 2.1 software (Applied Biosystems). We achieved an average genotyping call rate of 95.5%, with call rates ≥ 93.1% for each SNP with one exception (rs12733285 (82%)). All samples not genotyped using this method were directly sequenced using primers purchased from Invitrogen Life Technologies (primer sequences available upon request). Each PCR reaction included 5 μL of 10× PCR buffer (Invitrogen), 1.5 μL of 50mM MgCl, 5 μL of forward primer at 5mM concentration, 5 μL of reverse primer at 5mM concentration, 1 μL 10 mM dNTPs, 29 μL water, 0.5 μL Platinum Taq DNA polymerase (Invitrogen), and 60 ng of genomic DNA. PCR products were then cleaned using Montage PCR Centrifugal Filter Devices (Millipore, Billerica, MA) and sequenced on an ABI Prism 3100 Genetic

Analyzer. Cycle sequencing was accomplished using Big Dye Terminator v3.1 chemistries (Applied Biosystems, Foster City, CA).

Our initial analysis indicated that rs12733285 did not achieve Hardy-Weinberg Equilibrium (HWE) in controls with an excess of homozygotes for this SNP. We selected a subset of individuals that were determined to be homozygous according to SDS 2.1 software, and performed direct sequencing to investigate the deviation. Upon sequencing, we discovered an additional A→T transversion 1 base-pair before (contig position 53412393) our SNP of interest (rs12733285). Due to this observation, we determined that rs12733285 should be dropped from our analysis because the additional SNP may change the fidelity of the TaqMan probe, thus skewing the accuracy of the genotyping platform and creating the HWE deviation. The additional SNP that was observed has not been previously described in the dbSNP database and may be segregating preferentially among African Americans.

Statistical Analysis

All statistical analyses were performed using Statistical Analysis Software (SAS Institute Inc. v. 9.1, Cary, N.C.). All tests were evaluated using a two-sided hypothesis test with statistical significance interpreted as having a p-value less than or equal to 0.05. Obesity was defined according to the current Centers for Disease Control (CDC) criteria (≥ 30.0 kg/m^2). Differences in age and obesity between prostate cancer cases and controls were tested using a Wilcoxon rank-sum test and chi-square test, respectively. Differences in the minor allele frequency (MAF) in these SNPs between FMHS controls and African American (when available) or African samples identified using NCBI's dbSNP database http://www.ncbi.nlm.nih.gov/projects/SNP/ were tested using chi-square tests. For each SNP, the observed genotype distribution among controls was tested for consistency with HWE expectations using Pearson's chi-square test. Unconditional logistic regression was used to determine whether genotypes within each SNP were associated with either prostate cancer or obesity (among controls), with additive, dominant and recessive models A post-hoc test comparing homozygotes for the minor allele and heterozygotes each to homozygotes for the major allele (the referent) was also performed. All single SNP models were run controlling for age and the estimated proportion of African ancestry for each study participant using the statistical software Structure(20). Multivariable models simultaneously adjusted for the effect of each SNP, including only SNPs within the same gene, age and ancestry. However, as adjustment for ancestry did not alter the calculated odds ratios, we report those adjusted only for age and other SNPs.

Adiponectin signaling status was assessed using the genotypes at two SNPs (rs1501299 and rs2241766) based on their suspected function in regulating circulating adiponectin concentrations(18). As such, we attempted to replicate prior findings, classifying subjects with the following genotype combinations as low signalers (276*GG/45*TT; 276*GT/45*TT; 276*GG/45*GT) and intermediate to high signalers with genotype combinations (276*TT/45*TT; 276*GT/45*GT; 276*GG/45*GG; 276*GT/45*GG; 276*TT/45*GG; 276*TT/45*GT) and then comparing the prevalence of these combinations between prostate cancer cases and controls.

Results

A number of key characteristics of FMHS participants related to the current investigation are reported in Table 1. The average age among the 475 African American participants genotyped for this study was 63.4 years (standard deviation (SD) of 10.0 years). The controls were significantly younger with a mean age of 62 years (SD=10.1) compared to 67 years (SD=8.6) among cases ($p<0.0001$). Approximately 32% of participants were considered obese, with no significant difference in the prevalence of obesity between cases (33%) and controls (31%). The absence of any significant association between obesity and diabetes with prostate cancer in this population has been reported previously(21). We found no difference in the mean proportion of African ancestry between FMHS cases and controls (~71%) as has also been reported (22). The median pre-diagnostic PSA level among cases was 6.2 ng/ml [interquartile range (IQR) 4.3-11.9 ng/ml]. Approximately, half of FMHS cases were treated surgically (48.1%) and 11% were diagnosed with high grade disease (Gleason sum 8-10).

Genotype distributions for nine of ten SNPs were consistent with HWE ($p\geq0.05$). The position of each SNP and minor allele frequency (MAF) among FMHS controls were reported and this MAF was compared to African American samples identified through the NCBI dbSNP database (Table 2). As expected, there were few differences in the MAF between groups. The MAF in rs10920531 was significantly higher in FMHS controls compared to the HapMap(23) Yoruba (YRI) population ($p=0.002$), used for comparison as data from an African American sample was unavailable in the NCBI database.

We found no significant differences in genotype frequency between prostate cancer cases and controls (Table 3). Furthermore, an analysis stratified by body mass index (<30 kg/m^2 and ≥ 30 kg/m^2) did not provide evidence for effect modification of the association between SNPs and prostate cancer by obesity (data not shown). Likewise, no association was observed between adiponectin signaling status and prostate cancer risk. Using genotype data from SNPs rs1501299 and rs2241766, the proportion of intermediate to high signalers was nearly identical among cases and controls (age-adjusted OR = 0.99; 95% CI = 0.57, 1.73).

Among FMHS controls, two SNPs in *ADIPOQ* (rs1501299 and rs822395) were significantly associated with obesity after adjustment for age ($p=0.03$ and $p=0.04$, respectively using an additive model) (Table 4). Homozygous subjects for the minor (T) allele in rs1501299 had more than twice the odds of obesity (OR = 2.29, 95% CI = 1.12-4.72) compared to homozygous subjects for the G allele. Heterozygotes also had greater odds of being obese compared to GG homozygotes, although this finding was not statistically significant (OR=1.36, 95% CI = 0.81-2.31). Adjustment for other genotyped SNPs in the *ADIPOQ* did not significantly alter these findings. Alternatively, the homozygotes for the minor (C) allele in rs822395 were 50% less likely to be obese (OR=0.51, 95% CI=0.25-1.03). However, the association was no longer statistically significant after adjustment for rs1501299 ($p=0.21$).

Discussion

Several variants in adiponectin gene (*ADIPOQ*) and the adiponectin type I receptor (*ADIPOR1*) have been recently implicated in breast and colorectal carcinogenesis(18;19). Specifically adiponectin signaling status, an assignment based on the genotype combinations of two SNPs in *ADIPOQ*, was associated with a 36% to 85% reduction in odds of breast cancer for intermediate to high signalers. Furthermore, a single SNP in *ADIPOR1* (rs7539542) was inversely associated with breast cancer (OR=0.57; 95% CI=0.35, 0.94) (18). The same panel of SNPs were analyzed in relation to colorectal cancer, showing a single SNP (rs266729) to be inversely associated (OR = 0.73; 95% CI=0.53, 0.99)(19).

In an attempt to extend these findings to prostate cancer, we genotyped these same SNPs in a population-based, case-control study of African American men and found no association between any SNP and prostate cancer risk. As a dual aim, we investigated the association between these variants and body mass in the controls and observed a single SNP (rs1501299) to be significantly associated with obesity after controlling for age and other genotyped SNPs within the same gene. Previous studies of the +276 G>T polymorphism (rs1501299) suggest that this SNP contributes to variability in circulating adiponectin, however, a recent meta-analysis indicated significant heterogeneity amongst studies(11). Contrary to the assumptions made by Kaklamani et al as to the role of rs1501299 on adiponectin levels, it has been surmised that rs1501299 is in linkage disequilibrium with an as of yet unidentified functional variant(11). Several studies have also examined the +276 G>T polymorphism in relation to insulin resistance, cardiovascular disease and obesity, producing mixed results(14;24-26). The inconsistencies may be attributed in part to differences in the racial composition of the populations under study and/or the presence of co-morbidities.

The current investigation is the first to examine the association between variants in genes involved in the adiponectin pathway, prostate cancer risk and obesity in African American men. Our results are consistent with two previous reports of obesity-related genes and prostate cancer risk in Caucasian men (27;28). Neither investigation reported any significant difference in genotype distribution between prostate cancer cases and controls in SNPs in *ADIPOQ*, *LEP* (leptin), *LEPR* (leptin receptor), *TNFα* (tumor necrosis factor α), *PPARγ* (peroxisome-proliferator-activated receptor *γ*), *TCF7L2* (transcription factor 7-like2) and *IL6* (interleukin 6).

Adiponectin is a 244-amino acid, collagen-like protein present in relatively high concentrations in humans, accounting for 0.01% to 0.05% of total plasma protein(29). It is the most plentiful of the adipokines, with levels approximately 3 times higher than that of leptin, a pro-inflammatory cytokine predominantly functioning in the control of appetite(30). Unlike other adipokines, circulating adiponectin is inversely related to body mass(31) and has a number of important functions which may influence progression of prostate cancer explaining the association between obesity and aggressive prostate cancer(9;32). Adiponectin possesses anti-proliferative properties demonstrated not only in prostate cancer, but also cancers of the breast, endometrium, liver and lung(33). The association between adiponectin and prostate cancer may be explained through its effects on

immune response, notably activation of several anti-inflammatory cytokines (IL10, IL1RA (IL1 receptor antagonist)) and suppression of NFkB dependent-TNF and IFN-γ production amongst other pro-inflammatory cytokines(30). Lastly, adiponectin concentrations have been linked to markers of insulin resistance and/or insulin sensitivity(34;35).

While our results do not support a contribution of genetic variability in *ADIPOQ* and *ADIPOR1* to prostate cancer risk in African Americans, there are several potential explanations for the discrepancy between these findings and those linking risk to adiponectin concentrations. Racial differences in the distribution of body fat, and the prevalence of specific features of the metabolic syndrome (hypertension, diabetes, hypertriglyceridemia, low HDL-cholesterol, abdominal obesity) have been well documented(36). The relationship between measures of body mass and adiposity with adiponectin concentrations has not been as thoroughly studied in African Americans as has been in Caucasians, particularly among men, leaving open the possibility of racial differences in the role of adiponectin and the initiation, promotion and progression of certain cancers. Studies have already demonstrated clear racial differences in the relationship between serum adiponectin and coronary heart disease risk(37). Furthermore, there has been some demonstration of racial heterogeneity in the contribution of genetics to circulating adiponectin levels (38) and insulin resistance (39;40). In a recent investigation, Wassel et al. observed that SNPs in *ADIPOQ* were strongly associated with serum adiponectin in whites, but not blacks participating in the Coronary Artery Development in Young Adults (CARDIA) study (41).

There are a few limitations which require consideration in the interpretation of our findings. First, the study was of limited power to detect modest differences between genotype and prostate cancer particularly when the “at-risk” allele frequency was less common in the control population. For example, with our sample size of 475 men, we were adequately powered (>80%) to detect a minimum two-fold increase in risk with a genotype frequency of 20% among controls (α=0.05). Furthermore, the strategy employed by Kaklamani et al to preferentially select those SNPs thought to be functionally relevant from a pool of SNPs tagging the two major haplotypes blocks within each gene among Caucasians may not capture the variation in these genes among African Americans. It is also possible that there are additional genes working in concert with the adiponectin genes which would need to be included to observe an effect on prostate cancer risk and clearly, testing for gene-gene interaction would necessitate a larger sample size. Despite these limitations, the Flint Men's Health Study remains one of the largest population-based investigations of prostate cancer conducted exclusively in an African American population. The comprehensive collection of clinical, epidemiologic and anthropometric measures, as well as the careful screening and follow-up of the control population are among the numerous strengths of the study design.

The results of the current investigation suggest that variation in the adiponectin gene associates with obesity, but is unrelated to prostate cancer risk in African American men. These findings suggest that the underlying biology of adiposity and prostate cancer is a complicated one and we still have much to discover about the factors which mediate this relationship. Further study, particularly among African Americans, is clearly justified given

the racial disparity in incidence of disease and outcomes post-diagnosis coupled with the epidemic increase in obesity in the U.S. across racial groups over the past few decades.

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Table 1

Baseline characteristics of 475* African American men participating in the FMHS. [Mean (SD) or (%)]

Characteristics	Prostate Cancer Cases (n=131)	Disease Free Controls (n=344)	P-value‡
Age (years)	67.2 (8.6)	62.1 (10.1)	<0.0001
BMI (%)			
<25 kg/m^2	24.8	33.4	
25-29.9 kg/m^2	41.9	35.8	
≥ 30 kg/m^2	33.3	30.8	0.18
Diabetes (%)	22.0	18.1	0.35
Family History (%)	21.4	17.0	0.17
% African Ancestry	70.4 (0.08)	70.6 (0.08)	0.78

*Results exclude missing data

‡Associated with either Chi-square or Wilcoxon test statistic

Table 2

Single Nucleotide Polymorphisms in the Adiponectin (*ADIPOQ*) and Adiponectin Receptor (*ADIPOR1*) in the Flint Men's Health Study.

Position	Gene	MAF (%) NCBI dbSNP†	MAF (%)* FMHS	p-value
-11365 C>G	*ADIPOQ*	18.2[a]	11.1	0.16
-4034 A>C	*ADIPOQ*	41.3[a]	44.5	0.64
-3964 A>G	*ADIPOQ*	20.0[b]	20.3	0.93
+45 T>G	*ADIPOQ*	4.1[c]	4.7	0.72
+276 G>T	*ADIPOQ*	27.1[d]	35.6	0.05
-11760 G>A	*ADIPOR1*	10.9[a]	11.7	0.94
+5843 C>T	*ADIPOR1*	43.5[a]	48.0	0.53
+10225 G>C	*ADIPOR1*	NA	35.9	--
+11363 A>C	*ADIPOR1*	28.9[b]	44.1	0.002

*Among controls

†Minor allele frequencies based on African or African American (AA) samples from:

[a]Perlegen AFD_AFR panel AA samples selected from the human variation panel of 50 African Americans (HD50AA-Coriell Cell Repository).

[b]International HapMap project samples Yorubian (YRI) population from Nigeria.

[c]Perlegen (P3) AA control samples from the Human Diversity Panel.

[d]SNP500panel (P1) anonymized samples with self-identified race as AA.

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Table 3

Odds of prostate cancer among African Americans by SNP genotypes in *ADIPOQ* and *ADIPOR1* (Adjusted Odds Ratios and 95% Confidence Intervals).

SNP	Genotype	Cases n (%)	Controls n (%)	Age-adjusted OR (95% CI)	P-value
ADIPOQ					
rs266729	CC	104 (79.4)	248 (78.9)	1.00	
	CG	24 (18.3)	62 (19.8)	0.90 (0.52,1.54)	0.70
	GG	3 (2.3)	4 (1.3)	1.54 (0.33,7.24)	0.59
					0.97[*]
rs822395	AA	50 (38.1)	112 (32.9)	1.00	
	AC	61 (46.6)	165 (48.5)	0.97 (0.61,1.53)	0.88
	CC	20 (15.3)	63 (18.5)	0.76 (0.44, 1.48)	0.39
					0.43
rs822396	AA	79 (60.3)	209 (63.0)	1.00	
	AG	48 (36.6)	111 (33.4)	1.35 (0.87, 2.11)	0.18
	GG	4 (3.1)	12 (3.6)	0.95 (0.30, 3.16)	0.95
					0.33
rs2241766	TT	114 (90.5)	297 (90.5)	1.00	
	TG	11 (8.7)	31 (9.4)	0.79 (0.37, 1.67)	0.54
	GG	1 (0.8)	0 (0.0)	--	--
rs1501299	GG	53 (40.5)	137 (42.4)	1.00	
	GT	61 (46.5)	142 (44.0)	1.06 (0.67, 1.66)	0.80
	TT	17 (13.0)	44 (13.6)	0.91 (0.47, 1.77)	0.79
					0.91
ADIPOR1					
rs2232853	GG	96 (73.9)	262 (77.7)	1.00	
	GA	33 (25.4)	71 (21.1)	1.07 (0.65, 1.75)	0.79
	AA	1 (0.8)	4 (1.2)	0.47 (0.05, 4.47)	0.51
					0.99
rs1342387	CC	41 (31.3)	87 (26.1)	1.00	
	CT	59 (45.0)	172 (51.7)	0.71 (0.44, 1.16)	0.17
	TT	31 (23.7)	74 (22.2)	0.91 (0.51, 1.62)	0.76

SNP	Genotype	Cases n (%)	Controls n (%)	Age-adjusted OR (95% CI)	P-value
					0.67
rs7539542	GG	54 (41.9)	140 (43.5)	1.00	
	GC	56 (43.4)	133 (41.3)	1.07 (0.68, 1.69)	0.77
	CC	19 (14.7)	49 (15.2)	0.87 (0.46, 1.65)	0.68
					0.81
rs10920531	AA	41 (31.3)	110 (33.1)	1.00	
	AC	66 (50.4)	151 (45.5)	1.13 (0.70, 1.81)	0.62
	CC	24 (18.3)	71 (21.4)	0.83 (0.45, 1.51)	0.53
					0.64

* p-value (trend) under an additive model *italicized*

Percentages may not equal 100 due to rounding.

Multivariable models exclude cases and controls with missing data.

Table 4

Odds of Obesity (defined as BMI ≥30 kg/m^2) by *ADIPOQ* and *ADIPOR1* SNP genotypes in FMHS control men.

SNP	Genotype	Obese n (%)	Non-Obese n (%)	Age-adjusted OR (95% CI)	p-value
ADIPOQ					
rs266729	CC	77 (77.0)	171 (79.9)	1.00	
	CG	22 (22.0)	40 (18.7)	1.21 (0.67,2.19)	0.52
	GG	1 (1.0)	3 (1.4)	0.89 (0.09-8.86)	0.92
					0.60[*]
rs822395	AA	41 (39.1)	71 (30.2)	1.00	
	AC	49 (46.7)	115 (49.4)	0.65 (0.39,1.11)	0.12
	CC	15 (14.3)	48 (20.4)	0.51 (0.25,1.03)	0.06
					0.04
rs822396	AA	70 (67.3)	139 (61.0)	1.00	
	AG	32 (30.8)	79 (34.7)	0.72 (0.43,1.21)	0.21
	GG	2 (1.9)	10 (4.4)	0.38 (0.08,1.79)	0.22
					0.10
rs2241766	TT	93 (90.3)	204 (90.7)	1.00	
	TG	10 (9.7)	21 (9.3)	1.09 (0.49,2.42)	0.83
	GG	0 (0.0)	0 (0.0)	--	--
rs1501299	GG	37 (36.6)	100 (45.1)	1.00	
	GT	45 (44.6)	97 (43.7)	1.36 (0.81,2.31)	0.25
	TT	19 (18.8)	25 (11.3)	**2.29 (1.12,4.72)**	0.02
					0.03
ADIPOR1					
rs2232853	GG	81 (78.6)	181 (77.4)	1.00	
	GA	21 (20.4)	50 (21.4)	1.01 (0.56,1.80)	0.98
	AA	1 (1.0)	3 (1.3)	0.91 (0.09,9.04)	0.93
					0.99
rs1342387	CC	29 (27.6)	56 (25.4)	1.00	
	CT	59 (56.2)	113 (49.6)	1.08 (0.62,1.88)	0.77
	TT	17 (16.2)	57 (25.0)	0.60 (0.30-1.22)	0.16

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SNP	Genotype	Obese n (%)	Non-Obese n (%)	Age-adjusted OR (95% CI)	p-value
					0.19
rs7539542	GG	44 (44.4)	96 (43.1)	1.00	
	GC	38 (38.4)	95 (42.6)	0.86 (0.51,1.45)	0.57
	CC	17 (17.2)	32 (14.4)	1.22 (0.61,2.46)	0.57
					0.79
rs10920531	AA	36 (35.3)	74 (32.2)	1.00	
	AC	45 (44.1)	106 (46.1)	0.87 (0.51,1.48)	0.61
	CC	21 (20.6)	50 (21.7)	0.90 (0.57,1.73)	0.74
					0.70

* p-value (trend) under an additive model *italicized*

Percentages may not equal 100 due to rounding.

Multivariable models exclude controls with missing data.