

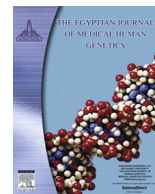
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Original article

Association of adiponectin gene (*ADIPOQ*) polymorphisms with measures of obesity in Nigerian young adultsOlusegun E. Ogundele^{a,c,*}, Khalid O. Adekoya^a, Abraham A.A. Osinubi^b, Awoyemi A. Awofala^c, Bola O. Oboh^a^a Cell Biology and Genetics Department, University of Lagos, Nigeria^b Anatomy Department, College of Medicine, University of Lagos, Nigeria^c Biological Sciences Department, Tai Solarin University of Education, Nigeria

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ABSTRACT

Background: The association of obesity with adiponectin gene has been reported in different populations with various inconsistencies. Data from Nigeria is very scanty on the association.**Aim:** We investigated possible associations of adiponectin gene (*ADIPOQ*) single nucleotide polymorphisms (SNPs) rs2241766 (+45T>G in exon 2), rs266729 (−11377C>G in promoter) and rs1501299 (+276G>T in intron 2) with body mass index (BMI), waist circumference (WC) and hip circumference (HC), in our cross-sectional study.**Subjects and methods:** SNPs in *ADIPOQ* were genotyped in 107 subjects (81 females, 26 males; mean age 22.2 years) by Sequenom MassARRAY. Notably, rs2241766 was removed for not reaching Hardy-Weinberg equilibrium. BMI was calculated (kg/m^2) while WC and HC were measured using standard procedures**Results:** Linear regression showed that variant rs1501299 was not associated with BMI, WC or HC but rs266729 was associated with increased measures of obesity involving BMI (recessive model; beta coefficient [β], 12.85; 95% confidence interval [CI], 6.47, 19.24, codominant model; GG, β , 13.08; 95% CI, 6.71, 19.46, GC, β , 1.04; 95% CI, −0.60, 2.68 and log-additive model; β , 2.117; 95% CI, 0.55, 3.68), WC (recessive model; β , 22.17; 95% CI, 7.11, 37.23 and codominant model; GG, β , 21.857; 95% CI, 6.74, 36.98, GC, β , −1.459; 95% CI, −5.34, 2.43) and HC (recessive model; β , 33.56; 95% CI, 15.41, 51.70, codominant model; GG, β , 34.171; 95% CI, 16.04, 52.30, GC, β , 2.771; 95% CI, −1.79, 7.34 and log-additive model; β , 5.466; 95% CI, 1.14, 9.80).**Conclusion:** This study in young Nigerian adults confirmed previously reported association of SNP −11377C>G with obesity measures in other populations.© 2017 Ain Shams University. Production and hosting by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Introduction

Obesity ($\text{BMI} > 30 \text{ kg}/\text{m}^2$) is a medical condition characterised by accumulation of excess body fats that may impair health and is currently recognized by the world health organization (WHO) as a chronic disease [1]. It is also a major risk factor for several chronic diseases, including stroke, hypertension, type 2 diabetes and different types of cancers [2–4]. Obesity is one of the leading risk factors for global mortality and morbidity and is a growing public health problem throughout the world [5]. In 2014, more

than 1.9 billion adults who are aged 18 years or more, were overweight globally and over 600 million of these adults were obese; thus indicating that 39% and 13% of the world population are overweight and obese respectively [6]. Prevalence of obesity among Nigerian adults ranges between 8.1% and 22.2% as revealed by a meta-analysis [7].

Genetic contribution to the aetiology of obesity has been well documented and it was reported that BMI, the WHO-adopted measure of obesity, has heritability estimate of 40–70% [8]. Although rare monogenic forms of obesity do exist, the polygenic form is more common, and the implicated genes thus far include, adiponectin, adiponectin receptors 1 and 2, among others [5,9–11]. Multiple genes (and polymorphisms within the genes) and environmental factors such as diet and lifestyle influence obesity but more clarification is needed to better understand the

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obesity aetiology [11]. Recently, multiple genetic loci have been strongly associated with obesity and obesity-related measures by association studies mostly in Caucasian populations [12,13].

Several independent association studies across populations worldwide have shown that some SNPs of *ADIPOQ* possess obesogenic effects albeit with inconsistent findings, which could be as a result of differences in ethnic populations, varying SNP selection criteria and study power [5,14–17]. The *ADIPOQ* obesity-associated variants span about 15.8 kb across three exons and are sited on chromosome 3q27 [18]. Among these variants the rs2241766, rs266729 and rs1501299 were studied often [14,19–21].

The *ADIPOQ* gene is exclusively expressed in the human adipose tissue and codes for the adiponectin found in the plasma. Plasma levels of adiponectin are known to be significantly decreased in patients with obesity [22,23]. Studies have associated mutations in *ADIPOQ* with human obesity cases and notably, a genome-wide association study (GWAS) showed that the *ADIPOQ* gene could account for 30–70% of the phenotypic variance for plasma adiponectin levels [5,10,24]. Several variants of *ADIPOQ* have been studied in relation to obesity, most with inconsistencies across different populations. Limited data on obesity risk alleles and their association with measures of obesity such as BMI, waist and hip circumferences exist in Nigeria. It was therefore the aim of this study to investigate in a population sample of Nigerian young adults the association of three previously described *ADIPOQ* variants with measures of obesity namely i) BMI; ii) waist circumference and iii) hip circumference.

2. Materials and methods

2.1. Study population

The sample cohort included healthy young adults of Nigerian descent ($n = 107$), mainly from Tai Solarin University of Education in Nigeria, being 81 females (75.7%) and 26 males (24.3%) aged between 18 and 30 years (mean age 22.2 years). Participants were randomly recruited from students at Tai Solarin University of Education, Nigeria between 2016 and 2017.

2.1. Ethical approval

The study was conducted in accordance with the declaration of Helsinki and was approved by the local institutional review committee and the Health Research Ethics Committee (HREC) of Lagos University Teaching Hospital (LUTH) with HREC assigned number ADM/DCST/HREC/APP/800. An informed consent was obtained from each participant before they participated.

2.2. Anthropometry

The anthropometric measurements including weight, height, waist and hip circumferences were obtained with individuals wearing light cloths and no shoes following standard procedures. Weight, height, waist and hip circumferences were taken using weighing scale, stadiometer and measurement tape respectively. Waist circumference was measured at the midpoint between the lower border of the rib cage (costal margin) and the iliac crest. Hip circumference was measured at the widest circumference over the buttocks and below the iliac crest. BMI was calculated as weight divided by square of height (kg/m^2).

2.3. DNA Isolation and SNPs genotyping

Blood samples were obtained from participants as dried blood spots (DBS) samples through fingerpicking. DBS samples were

spotted on Whatman FTA[®] cards (Whatman Inc., Brentford, UK) and were dried for 24 h at room temperature according to the method of Choi et al. [25]. They were then kept in separate clean zipper bags and stored at room temperature until analysis. Genomic deoxyribonucleic acid (DNA) was isolated from DBS samples using Zymo Research (ZR) DNA Card Extraction Kits following manufacturer's protocol. SNPs were amplified by polymerase chain reaction (PCR). PCR-specific and single-base extension primer sequences used for SNP amplification are provided in Table 1. *ADIPOQ* rs2241766, rs266729 and rs1501299 were genotyped by using Sequenom MassARRAY Genotyping System (Sequenom, San Diego, CA, USA) using previously described methods [26]. The genotyping efficiency was >92%.

2.4. Statistical analysis

Hardy-Weinberg equilibrium was tested using an exact test (HWExact) implemented in the R 3.1.3 package. Continuous data were summarized as mean \pm standard error. Statistical analyses were performed using SNPAssoc package implemented in the R package. We applied linear regression models to test the association of individual.

SNPs with obesity-related quantitative traits: BMI, WC and HC. The multivariable models were adjusted for age and gender. These regression models were implemented under four different genetic models: a codominant model that defines the three genotypes separately, a dominant model that grouped the heterozygous with the homozygous for the minor allele, a recessive model that grouped the heterozygous with the homozygous for the major allele and a log-additive model assigning a score counting the number of minor alleles with 0, 1, and 2 given to the homozygote for the major allele, the heterozygote, and the homozygote for the minor allele respectively. Only the recessive, the codominant and the log-additive models are presented in this report as these were the models with the lowest Akaike information criteria. Bonferroni correction of the significance values was used to correct for multiple testing on multiple markers. All P values can be multiplied by 3 (the total number of SNPs used) to give Bonferroni-adjusted P values. The sample size and power of the study was calculated by using Quanto version 1.2.4 software.

3. Results

Table 2 summarises population characteristics of the studied sample. Among the total participants ($N = 107$), 75.7% were

Table 1
SNP amplification and extension primer sequences.

dbSNP rs number	Marker	Primer sequence (5' → 3')
rs1501299	+276G>T	Forward primer
		ACGTTGGATGCTCTTTCATCACAGACCTCC
		Reverse primer
		ACGTTGGATGTCCTCTGTCTAGGCCCTAG
rs266729	-11377C>G	Extension primer
		AGGCCTTAGTTAATAATGAATG
		Forward primer
rs2241766	+45T>G	ACGTTGGATGATGTGTGGCTTGCAAGAACC
		Reverse primer
		ACGTTGGATGACCTTGGACTTCTTGGCAC
		Extension primer
rs2241766	+45T>G	GTCATGTTTTGTTTTGAAG
		Forward primer
		ACGTTGGATGGACAGTGCACATGTGGATTC
		Reverse primer
rs2241766	+45T>G	ACGTTGGATGCCTTGAGTCGTGGTTCCTG
		Extension primer
rs2241766	+45T>G	GTGGTTCCTGTGCATG

Table 2
Characteristics of the study sample and comparison between the sexes.

Variables	Total	Females	Males	P
N (%)	107	81	26	
Age (years)	22.23 (2.61)	22.19 (2.69)	22.35 (2.35)	0.793
Weight (kg)	59.20 (10.76)	59.33 (11.74)	58.80 (7.06)	0.096
Height (m)	1.66 (0.08)	1.64 (0.06)	1.72 (0.08)	<0.001
BMI (kg/m ²)	21.63 (3.70)	22.13 (3.87)	19.80 (1.88)	0.005
WC (cm)	75.89 (8.13)	76.08 (8.89)	75.33 (5.32)	0.071
HC (cm)	93.88 (9.84)	94.63 (10.74)	91.58 (5.89)	0.063
Underweight (18.5 ≤ BMI < 25 kg/m ²)*	18 (16.82)			
Normal (18.5 ≤ BMI < 25 kg/m ²)*	76 (71.03)	56 (69.14)	20 (76.92)	
Overweight (25 ≤ BMI < 30 kg/m ²)*	9 (8.41)	8 (9.88)	1 (3.85)	
Obesity (BMI ≥ 30 kg/m ²)*	4 (3.74)	4 (4.94)	0 (0)	

Abbreviations: N, number of individuals; BMI, body mass index; WC, waist circumference; HC, hip circumference. Data presented as mean (standard deviation) for continuous anthropometric variables and as N (%) for categorical variables (*).

females and 24.3% were males. The mean age of the 81 female and 26 male participants was 22.19 ± 2.69 years and 22.35 ± 2.35 years, respectively. The sample included 18 underweight subjects (16.82%), 76 normal-weight (71.03%), 9 overweight (8.41%) and 4 obese subjects (3.74%). BMI values were significantly higher in female participants than in males. There were no significant differences in the waist circumference and hip circumference in female participants compared with the male participants.

Genotypes and allele frequencies are detailed in Tables 3–5 for BMI, HC and WC respectively. There was no evidence of any deviation from the Hardy–Weinberg equilibrium for both *ADIPOQ* SNPs rs1501299 and rs266729, but rs2241766 failed to reach Hardy–Weinberg equilibrium and was removed from the analysis. Table 3 displays the association between *ADIPOQ* SNPs and BMI in three genetic models. Minor allele frequencies were rs1501299T:0.368, rs266729G:0.119. Statistically significant association of one variant *ADIPOQ* SNP rs266729 with BMI under the recessive model ($p = 0.0002$), codominant model ($p = 0.0004$) and the log-additive model ($p = 0.0095$) was found. The adjusted mean BMI (kg/m²) values for the rs266729 SNP were 20.98 ± 0.37 for participants with the C/C genotype, 22.02 ± 0.85 for those with the C/G genotype, and 34.06 ± 0.01 for those with the G/G genotype, and these differences were statistically significant. Although the mean BMI values for the GG, GT and TT genotypes of *ADIPOQ* rs1501299 were 21.16 ± 0.66, 21.65 ± 0.52 and 21.11 ± 0.89 respectively, these differences were not statistically significant under any of the genetic models.

We also tested the associations between the SNPs and each of hip circumference and waist circumference under three genetic models. Interestingly, only SNP rs266729 showed significant association with hip circumference under the recessive model ($p = 0.0005$), codominant model ($p = 0.0011$) and the log-additive

model ($p = 0.0151$) – Table 4, and with waist circumference under the recessive model ($p = 0.0049$) and codominant model ($p = 0.0149$) – Table 5. The adjusted mean hip circumference (cm) values for the rs266729 SNP were 91.83 ± 1.02 for participants with the C/C genotype, 94.60 ± 2.46 for those with the C/G genotype, and 126.00 ± 0.00 for those with the G/G genotype. These observations were significantly different under the three genetic models. However, for rs1501299, there was no significant difference in the mean hip circumference of participants. The waist circumference (cm) values for the CC (75.14 ± 0.91), GC (73.68 ± 1.76), and GG (97.00 ± 0.01) genotypes significantly differed in rs266729, but not for the GG (76.56 ± 1.40), GT (74.83 ± 1.21) and TT (72.08 ± 2.07) genotypes in rs1501299 after adjustment for age and gender. Minor allele frequencies were rs1501299T:0.372, rs266729G:0.121 for HC and rs1501299T:0.371, rs266729G:0.117 for WC.

The results from the analysis of the overall population haplotype block frequency for *ADIPOQ* rs266729 and rs1501299 revealed that the CG haplotype (0.378) was seen frequently compared with the CT (0.286), GG (0.070) and GT (0.013) haplotypes and significantly associated with BMI ($p < 0.001$). The linkage disequilibrium between rs266729 and rs1501299 was low ($D' = 0.619$ and $R^2 = 0.033$).

4. Discussion

The study investigated genetic changes in *ADIPOQ* gene in relation to obesity measures involving BMI, waist circumference and hip circumference in a sample of young Nigerian adults and found a significant association between these measures and rs266729 SNP (−11377C>G) in this population. However, the other SNP

Table 3
Associations of SNPs with BMI in three genetic models.

Trait					Genetic Models						
SNP	Chr.	Genotypes	M/m	HWE P	BMI (SE); kg/m ²	Recessive β (95% CI)	P [*]	Codominant β (95% CI)	P [*]	Log-additive β (95% CI)	P [*]
rs1501299	3	GG:36	G/T	0.680	21.16 ± 0.66	−0.296 (−2.38, 1.79)	0.6460	0.491 (−1.12, 2.11)	0.8070	0.098 (−0.96, 1.15)	0.8560
		GT:38			21.65 ± 0.52						
		TT:13			21.11 ± 0.89						
rs266729	3	CC:68	C/G	1.000	20.98 ± 0.37	12.85 (6.47, 19.24)	0.0006	1.04 (−0.60, 2.68)	0.0012	2.117 (0.55, 3.68)	0.0285
		GC:19			22.02 ± 0.85						
		GG:1			34.06 ± 0.01						

BMI according to genotypes. Data are means ± SE. All P values were two sided). βs and 95% CI were calculated using linear regression with genotypes as independent variables. Chr., chromosome.

Bold indicates significant association.

* Indicates Bonferroni corrected values.

Table 4
Associations of SNPs with HC in three genetic models.

Trait						Genetic Models					
SNP	Chr.	Genotypes	M/m	HWE P	HC (SE); cm	Recessive β (95% CI)	P^*	Codominant β (95% CI)	P^*	Log-additive β (95% CI)	P^*
rs1501299	3	GG:36	G/T	0.680	92.89 \pm 2.03	–4.609 (–10.35, 1.13)	0.3576	1.2089 (–3.18, 5.60)	0.2586	–1.207 (–4.15, 1.74)	0.4239
		GT:41			94.10 \pm 1.06						
		TT:13			88.92 \pm 2.90						
rs266729	3	CC:70	C/G	1.000	91.83 \pm 1.02	33.56 (15.41, 51.70)	0.0015	2.771 (–1.79, 7.34)	0.0033	5.466 (1.14, 9.80)	0.0453
		GC:20			94.60 \pm 2.46						
		GG:1			126.00 \pm 0.00						

HC according to genotypes. Data are means \pm SE. All P values were two sided). β s and 95% CI were calculated using linear regression with genotypes as independent variables. Chr., chromosome.

Bold indicates significant association.

* Indicates Bonferroni corrected values.

Table 5
Associations of SNPs with WC in three genetic models.

Trait						Genetic Models					
SNP	Chr.	Genotypes	M/m	HWE P	WC (SE); cm	Recessive β (95% CI)	P^*	Codominant β (95% CI)	P^*	Log-additive β (95% CI)	P^*
rs1501299	3	GG:36	G/T	0.680	76.56 \pm 1.40	–3.568 (–8.23, 1.09)	0.4116	–1.731 (–5.30, 1.84)	0.6387	–2.117 (4.47, 0.24)	0.2451
		GT:40			74.83 \pm 1.21						
		TT:13			72.08 \pm 2.07						
rs266729	3	CC:70	C/G	1.000	75.14 \pm 0.91	22.17 (7.11, 37.23)	0.0147	–1.459 (–5.34, 2.43)	0.0447	0.9600 (–2.72, 4.64)	0.6103
		GC:19			73.68 \pm 1.76						
		GG:1			97.00 \pm 0.01						

WC according to genotypes. Data are means \pm SE. All P values were two sided). β s and 95% CI were calculated using linear regression with genotypes as independent variables. Chr., chromosome.

Bold indicates significant association.

* Indicates Bonferroni corrected values.

rs1501299 (+276G>T) showed no significant relationship to obesity measures in this population.

The association of –11377G allele with a higher BMI, waist and hip circumferences, suggests that this biomarker is possibly implicated in obesity and abdominal body fat gain. Interestingly, it has been documented that the presence of abdominal adipose tissue may modulate the contributory effect of another SNP, rs1501299 (+276G>T) in the intronic region of the *ADIPOQ* gene on plasma adiponectin concentrations [27]. While this study did not study adiponectin concentration nor establish any significant association between rs1501299 and obesity measures (as discussed below), the present association study suggests that –11377G carriers of the promoter *ADIPOQ* gene variant could be at greater risk of general and regional fat increase especially among young Nigerian population. In a similar study on two *ADIPOQ* promoter SNPs, Dolley and colleagues [15] observed that –11391G>A polymorphism was associated with an increased waist circumference but not BMI. Accordingly, an inverse association between BMI and plasma adiponectin levels has been previously reported [28], and the adiponectin itself is a product of *ADIPOQ* gene.

The potential association between *ADIPOQ* rs1501299 and obesity measures have been investigated in several studies [19,29–31]. Some of these studies have reported a significant association between them [19]; however, other studies have failed to find any associations [29–31]. We found no significant association between *ADIPOQ* rs1501299 and the three measures of obesity: BMI, waist and hip circumferences. This is in line with the findings from several other studies including the Framingham Offspring Study [31], the Heritage Family Study [30], the Oulu Diabetic Study [30], and the study involving black and white women [29]. Moreover, our result is not consistent with the findings from a sample of Egyptian young adults where significant associations were

found between *ADIPOQ* rs1501299 and some obesity measures including BMI, waist to hip ratio and mid upper arm circumference [19]. These inconsistencies in results may be explained by the differences in the genetics or epigenetics of the respective study populations.

It is particularly noteworthy that while the *ADIPOQ* polymorphisms involving rs2241766, rs266729 and rs1501299 were found to be associated with obesity and obesity-related traits in several studies in American, African, Asian and European populations, both in children, young adults and older adults [5,14,19], other findings on the genetic association of these SNPs with obesity parameters have been somewhat inconsistent across different groups thus warranting the need for replication studies across different populations, age groups or genders [5]. In this cohort, frequencies for both the rs1501299 and the rs266729 polymorphisms, but not the rs2241766 polymorphism were in Hardy-Weinberg equilibrium. The frequencies of risk alleles and genotypes in *ADIPOQ* rs1501299 and rs266729 slightly differed from previously reported data in other populations [15,19,32]. This difference is expected since there may be variability in frequencies of polymorphisms in different populations, even within the same ethnicity [16].

Our study has some strengths and limitations. To the best of our knowledge, this is the first Nigerian study that provides data on the association between *ADIPOQ* genetic polymorphisms and obesity measures. In terms of limitation, we did not collect data on food and nutrient intake, physical activity, smoking and alcohol status and some other environmental covariates that may act as moderators. These variables may be considered for further studies investigating gene-environment interaction. In addition, the SNPs analyzed in the present study were not powered to detect rare variants; there may be additional genes working in concert with adiponectin-related genes which would need to be included to

observe an effect and such would require a much larger sample size. Moreover, linkage analyses involving other variants of the *ADIPOQ* gene could be carried out in future studies to help to provide clearer understanding of the influence of variations at *ADIPOQ* gene on obesity measures in Nigerian young adults.

Another limitation is that measurement error may occur in any of the outcome variables or the anthropometric indices used in this study, however, reliability was ensured as much as possible by performing all measurements twice and, if the measurements differed by more than a pre-specified value, a third measurement was taken and the average of all three measurements used. This study also had limited power to detect low differences between genotypes and some of the wide confidence intervals (Cis) reported were mostly due to the small sample size. Finally, our sample is not nationally representative and it is uncertain if our results could be generalized to other ethnicities.

We conclude that the GG genotype of the promoter *ADIPOQ* rs266729 polymorphism was associated with each of BMI, waist circumference and hip circumference but no association was found between rs1501299 and the obesity measures in Nigerian young adults. This supports current knowledge regarding the putative influence of *ADIPOQ* SNPs on body corpulence. Our results should be considered preliminary, and are likely to contain false positives/negatives, thus, replication studies of independent samples involving different ethnic groups in Nigeria are required.

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