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Association Study of Candidate Gene Polymorphisms and Obesity in a Young Mexican-American Population from South Texas

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Abstract

Background and Aims—Obesity is increasingly a health problem and a risk factor for diabetes in young Mexican-American populations. Genetic association studies in older, mostly non-Hispanic populations have reported that polymorphisms in the candidate genes *HSD11B1, CRP, ADIPOQ, PPARG, ANKK1, ABCC8* and *SERPINF1* are associated with obesity or diabetes. We analyzed the polymorphisms rs846910, rs1205, rs1501299, rs1801282, rs1800497, rs757110 and rs1136287in these candidate genes, for association with obesity and metabolic traits in a young Mexican-American population from south Texas.

Methods—Genotyping of the seven common SNPs were performed by allelic discrimination assays in 448 unrelated Mexican Americans (median age = 16 years) from south Texas. χ^2 tests and regression analyses using additive models were used for genetic association analyses adjusting for covariates; *p* values were corrected for multiple testing by permutation analyses.

Results—rs1800497 (*ANKK1*) shows association with waist circumference ($p = 0.009$) and retains the association ($p = 0.03$) after permutation testing. Analysis of metabolic quantitative traits shows that rs846910 (*HSD11B1*) was associated with HOMA-IR ($p = 0.04$) and triglycerides ($p = 0.03$), and rs1205 (*CRP*) with HOMA-IR ($p = 0.03$) and fasting glucose levels ($p = 0.007$). However, the quantitative traits associations are not maintained after permutation analysis. None of the other SNPs in this study showed associations with obesity or metabolic traits in this young Mexican-American population.

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The authors state that there are no conflicts of interest to disclose.

Conclusions—We report a potential association between rs1800497 (linked to changes in brain dopamine receptor levels) and central obesity in a young Mexican-American population.

Keywords

Obesity; Diabetes; Polymorphism; Mexican-American; Genetic association

Introduction

Obesity and overweight represent health problems that are risk factors for the development of other chronic conditions such as diabetes, cancer and cardiovascular disease (CVD) (1). According to the information provided by the National Health and Nutrition Examination Survey (NHANES) in the U.S., the prevalence of obesity in persons >20 years is 33.9%. However, this number increases to 39.3% in the Mexican-American population (2). It has also been suggested that Mexican immigrants have a 64% higher chance to develop the obese phenotype than US-born whites (3). In the southernmost region of Texas, in the Rio Grande Valley (RGV), a recent socioeconomic study shows that prevalence of obesity in an older Mexican-American population ranges from 55.5–57%, the highest rate observed nationwide (4). In younger Mexican Americans, the increasing rates of obesity, metabolic syndrome (MetS) or type 2 diabetes (T2D) are disproportionately higher than in other populations (5,6). In a study of adolescent Mexican-Americans in RGV, 50% are either overweight or obese, 41% have central obesity and 27% exhibited insulin resistance (7). Environmental factors such as reduced physical activity, intake of energy-dense food and/or cultural and socioeconomic factors play an important role in the development of obesity (8). However, evidence from recent studies suggests that genetic factors account for 40–90% of the body mass index (BMI) variations among populations (9). The future of medicine, whether it is prevention, diagnosis, and therapeutic care for human diseases includes personalized genomics. This involves the identification of genetic factors that confer risk of susceptibility to obesity and related metabolic abnormalities in individuals. More than 127 biologically relevant candidate genes with DNA variations associated with obesity-related phenotypes have been identified (10). In the present study we analyzed the association of seven single nucleotide polymorphisms (SNPs), rs846910, rs1205, rs1501299, rs1801282, rs1800497, rs757110 and rs1136287, with obesity and related metabolic traits in a young Mexican-American cohort of 448 non-related individuals. These seven SNPs were chosen because they have been shown to be associated with obesity or obesity-related phenotypes in previous studies or are located in well-established obesity candidate genes (Table 1). The chosen candidate genes are *HSD11B1*, *CRP*, *ADIPOQ*, *PPARG*, *ANNK1*, *ABCC8* and *SERPINF1*. Individuals from this cohort include previously recruited RGV Mexican-American adolescents (7) as well as newly recruited Mexican-American college students. None were from the older Mexican-American Cameron County Hispanic Cohort of RGV (4).

Subjects and Methods

Subjects and Clinical Measurements

A total of 448 volunteers from the Brownsville population (southern Texas) consented to participate. All subjects (and parents for subjects <18 years) provided informed consent prior to participation in the study. Consent was specifically obtained to save identified DNA samples for genetic studies. All studies were approved by the IRBs (UTHSC-Houston and UTB). This study was conducted under the basic principles of the Declaration of Helsinki. Inclusion criteria include Mexican-American etiology. First-degree familiars were excluded from statistical analysis.

Fasting blood samples were drawn from all subjects into EDTA-coated tubes and red blood cells separated by centrifugation. The supernatant comprising plasma and the buffy coat layer including white blood cells were aspirated separately and frozen immediately in aliquots at −70°C.

Anthropometric measurements including height, weight, and waist circumference (WC) were done according to standardized protocols. WC cut-offs for central obesity were calculated using the parameters proposed by Taylor (11) for individuals <20 years. For subjects 21 years and older, the values were >88 cm for women and >102 cm for men (12). BMI was calculated according to the formula: weight in kilograms (kg)/height in meters (m^2). For subjects <20 years of age, calculations were made converting to age- and gender-standardized percentiles based on the U.S. Centers for Disease Control and Prevention 2000 growth charts (http://www.cdc.gov/growthcharts/), which are not race specific. Results were classified as normal weight if BMI was <85th percentile, overweight if BMI was ≥85th and <95th percentile, or obese if BMI was ≥95th percentile. For subjects 20 years of age and older, BMI 25–29.9 kg/m^2 was classified as overweight and BMI ≥30 kg/m^2 as obese (12).

Metabolic measurements include fasting blood glucose, blood pressure, homeostasis model of insulin resistance (HOMA-IR) and triglycerides. HOMA-IR was calculated by the formula (fasting insulin [μU/ml] × fasting glucose [mmol/l]/22.5) and classified as insulin resistant if the result was ≥3.16 (13).

DNA Extraction and Genotyping

DNA was extracted from 1 ml of blood sample using a QIAmp DNA Mini Kit (Qiagen, Valencia, CA) according to the manufacturer's protocol. DNA quantification was carried out using a Nanodrop spectrophotometer (Thermo Scientific, Waltham, MA) and the amount of recovered DNA was determined using 96-well plates prepared with 50 ng per well of DNA. These plates were left to dry overnight and then stored at −20°C until used. TaqMan SNP Genotyping Assays were used for genotyping in the Step One Plus Real-Time PCR system (Applied Biosystems, Carlsbad, CA). Five-μl PCR reactions were performed using 1 μl DNA (50 ng/μl) or ddH_2O for negative controls, 0.125 μl probe (20 μmol/L), and 2.25 μl Master Mix (20 μmol/l) (Applied Biosystems). The program consisted of an initial denaturation step at 95°C for 10 min followed by 40 cycles of 95°C for 15 sec, 60°C for 1 min and a final extension step of 60°C for 30 sec.

Statistical Analysis

Data are presented as mean and ± standard deviation (SD). Genotype distributions of the seven SNPs were analyzed for deviation from Hardy-Weinberg equilibrium using χ^2 test. Logistic regression analysis assuming an additive model was performed to determine the association between SNPs and BMI as an obesity measure and WC as central obesity value. The associations were adjusted for gender and age as covariates. Odds ratios (ORs) with 95% confidence intervals (CIs) are presented in the tables with respect to the risk alleles; *p* value of 0.05 was considered significant and empirical significance levels were computed by permutation test. Linear regression analysis was used for quantitative traits under an additive genetic model adjusted for age, gender and BMI. All statistical analysis were performed using PLINK v.1.07 (http://pngu.mgh.harvard.edu/~purcell/plink) (14), and SPSS v.17.0 (SPSS, Chicago, IL).

Quanto Software (v.1.2.4) (http://hydra.usc.edu/gxe/) was used to calculate the power of the sample. A 39% prevalence of obesity among Mexican-Americans (2), additive genetic model for any SNP and a MAF of at least 30% shows that the sample size of the present study had an 80% power with an $\alpha = 0.05$ to detect an effect size of 1.47.

Results

Clinical and anthropometric characteristics are shown in Table 2. The median age of the cohort was 16 years and was composed predominately of female subjects (65%). Based on median value of BMI, the male population in our study is slightly overweight (BMI 25.4). According to BMI values, 28.3% of the sample population is obese, and 21.3% are overweight. However, a total of 53.1% of the subjects have WC measurements correlated with central obesity and considered a risk factor for MetS.

Distributions of the genotype and allele frequencies of the seven SNPs were in accordance with Hardy-Weinberg equilibrium using χ^2 test (Table 3). The *ANKK1* SNP rs1800497 (G/A) shows a higher frequency of the (A) allele in subjects with obese BMI values than in those with non-obese BMI values ($p = 0.04$) as also when comparing subjects with central obesity vs. subjects with no central obesity ($p = 0.009$) and after adjusting for age and gendere (Table 4). After using permutation test to empirically derive significance corrected for multiple testing, only association with WC values of central obesity remained significant ($p = 0.03$). There were no trends of association found for the remaining six SNPs with BMI or WC.

Analysis of the quantitative metabolic traits shows statistical significance for the association between the *HSD11B1* SNP rs846910 with HOMA-IR and triglyceride values ($p = 0.04$ and $p = 0.03$, respectively). For the *CRP* SNP rs1205, a statistical significance was also observed with HOMA-IR and fasting plasma glucose levels ($p = 0.03$ and $p = 0.007$, respectively) (Table 5). Nevertheless, after permutation testing, none of the values of associations with quantitative traits remained statistically significant. No associations were observed for the other SNPs.

Discussion and Conclusions

Although 21.3% of the young Mexican-American population evaluated in this study is overweight, only 28.3% are obese as defined by BMI. However, when WC is considered, 53% of the subjects are classified as being centrally obese. These results, as well as results from an earlier study, suggest that WC measurement may be a more effective measurement in young Mexican-Americans to assess obesity and metabolic risk than BMI (7). Rankinen et al. (2005) summarized obesity and/or obesity-related phenotype associations of various SNPs in the candidate genes in this study, in multiple populations (15). We summarized in Table 1 (16–30) previously described associations between obesity and obesity-related phenotypes and the selected SNPs in this study. To date, limited or no information exists in the literature regarding the associations of rs846910, rs1205, rs757110 and rs1136287 located in *HSD11B1, CRP, ABCC8* and *SERPINF1*, respectively, with obesity in the Mexican-American population.

The *Taq*IA polymorphism (A1 allele) originally identified in the dopamine receptor (*DRD2*) has been associated with lower levels of dopamine receptors (31–35). The *Taq*I A1 allele is associated with obesity as well as eating disorders and addictive behavior in heterogeneous analyzed groups (27–30,32,36,37). It has been reported that dysfunction in the dopamine signaling pathway (involved in food reward) in the brain may contribute to obesity (32). Recently, it was reported that *Taq*IA (A1 and A2 alleles) polymorphism, now referred to as rs18000497, is located 9489 bp downstream from the 3′ end of *DRD2* in the last exon of the adjacent gene ankyrin repeat and kinase domain containing 1 *(ANKK1)* transcribed in the opposite direction (38). Although this SNP has been shown to affect *DRD2* expression, we thus refer to rs1800497 as a SNP in *ANKK1*. The rs1800497 (A) allele corresponds to the *Taq*I (A1) allele and the rs18700497 (G) allele corresponds to the *Taq*I (A2) allele.

In this study, an association was observed with the (A) allele of rs1800497 and central obesity in a young Mexican-American population. Considering the genetic admixture of this Mexican population, further structured association studies will be needed to validate this potentially novel genetic association. From a biological perspective, the dopamine neurotransmitter is important in food intake regulation via the mesolimbic reward circuit of the brain (32) and higher BMIs are associated with a lesser number of brain dopamine receptors (37). However, despite the plausible biological explanation, association between obesity and the rs1800497 SNP is not universal, and these results have not been replicated in Pima Indian, Nauruan and Australian populations (39,40). The association of this polymorphism in obese subjects and binge eaters with high sensitivity to food reward in a mixed Canadian population is also not fully understood (41). Among risk factors, glucocorticoid excess is a well-known cause of obesity (42). Recent evidence suggests that even if circulating levels of glucocorticoids are not elevated, excessive production of glucocorticoids in peripheral tissues is associated with obesity and insulin resistance (43,44) The enzyme 11 beta hydroxysteroid dehydrogenase Type 1 (HSD11B1), which converts the inactive cortisone into the active cortisol, is expressed in insulin-sensitive tissues such as adipose tissue, muscle, liver and central nervous system (45). Elevated levels of HSD11B1 expression in adipose tissue have been shown to be associated with obesity, T2D, and changes in insulin sensitivity in several populations (43,46). Allelic variants and mRNA levels of *HSD11B1* have been previously associated with obesity, insulin sensitivity, hypertension and T2D (26,47,48).

In the present study we observed a trend towards association between the (A) allele of rs846910 (*HSD11B1*) and HOMA-IR and triglycerides values, which are predictive measures for MetS. In Pima Indians, the (A) allele is associated with increased insulin resistance as well as T2D. Because Mexican-Americans have Native American heritage, the observed trend of association suggests the possibility of shared genetic susceptibility to diabetes through variations in *HSD11B1*.

C-reactive protein (CRP) is an important inflammatory marker, and circulating levels of this protein may have a prognostic value in identifying subjects with increased risk of developing T2D, obesity and or insulin resistance in Caucasian, African-American and Peruvian populations (49,50). It has also been shown that CRP levels may be modified by mutations in the *CRP* gene (51). Although we observed an association between the (T) allele of rs1205 with HOMA-IR and fasting glucose, the statistical significance did not remain after correction for multiple testing.

One of the most studied obesity and obesity-related phenotype candidate genes is the peroxisome proliferator-activated receptor-γ2 (*PPARG)* because it plays a role as the master transcriptional regulator for adipocyte differentiation and metabolism genes. The rs1801282 SNP (also known as Pro12Ala) is commonly associated with obesity and diabetes in several populations, ethnic groups and meta-analysis studies (15,52). Previous reports of association between the polymorphism rs1801282 (Pro12Ala) of the *PPARG* gene and obesity in the Mexican-American (17,19) or Mexican-Mestizo populations (16) could not be replicated in this study. However, the minor allele (G) frequencies were similar between this cohort and other Caucasian and Hispanic cohorts (10–13.5%) (19,53–55). The most important differences from the previous reports (Table 1) and this study are the ages of the subjects. In this cohort the median age was 16 years, a relatively young and healthy population when compared to the other reports with median age values from 38.7–58.6 years. Nevertheless, a future study in this Mexican-American population including older participants could verify the previously reported associations of *PPARG* SNPs with obesity. Furthermore, other studies show only association between the *PPARG* SNP and obesity in a gender-specific manner in Mediterranean (Greek and Tunisian) populations (56,57), which we did not

observe in this study. A novel HuGE meta-analysis shows that *PPARγ*rs1801282 was associated with a reduction in T2D risk; however, they also report a moderate level of heterogeneity, which can lead to variations among ethnic groups (52). A few studies show associations not with T2D, but with metabolic changes associated with MetS (58,59). However, we did not observe associations with metabolic traits in this study.

The adiponectin gene *(ADIPOQ)* encodes a major adipokine secreted from white adipose tissue and plays an important role in energy metabolism and immune response. Associations of polymorphisms in this gene with obesity and insulin resistance have been investigated in Caucasian and Hispanic populations (21,60,61). The pancreatic β-cell K_{ATP} channel is composed of two essential subunits: the Kir6.2 and the sulfonylurea receptor 1 (SUR1) and are encoded by the two adjacent genes, the potassium inwardly-rectifying channel, subfamily J, member 11 (*KCNJ11)* and the ATP-binding cassette, subfamily C member 8 (*ABCC8),* respectively (62). This channel plays a central role in glucose-stimulated insulin secretion from pancreatic beta cells, and meta-analysis studies show that polymorphisms in *KCNJ11* have been associated with T2D (63). Polymorphisms in *ABCC8* have been correlated with hyperinsulinemic hypoglycemia and T2D in Japanese and Caucasian populations (64,65). The serpin peptidase inhibitor, clade F, member 1 (SERPINF1), also known as anti-plasmin pigment epithelium derived factor (PEDF) is an adipokine secreted by adipocyte cells with levels comparable to that of adiponectin. Although, at first, it was isolated as a neurotrophic factor capable of converting retinoblastoma tumor cells into differentiated nonproliferative neurons, novel studies showed that expression of SERPINF1 in adipocyte cells correlates with obesity and insulin resistance in murine models (66,67). It is also highly expressed in hepatocytes, and accumulation of triglycerides in PEDF null mouse hepatocytes has been reported and postulated as one of the factors underlying fatty liver disease in MetS and T2D (67). Serum PEDF levels have been positively associated with adiposity in diabetic Japanese and obese Caucasian subjects (68,69). The *ADIPOQ* SNP rs1501299 has been analyzed previously in Mexican-American population by Richardson (21), but no association was found with obesity, T2D and HOMA-IR. Our study confirms this finding. rs757110 (Ala1369Ser) in *ABCC8* is associated with T2D in Caucasian populations (65). However, other SNPs in *ABCC8* in large-scale association studies in Caucasian subjects from the UK show no association with diabetes (63). Thus, the lack of associations with obesity and metabolic traits in this study and previous reports for rs1501299 (*ADIPOQ)* (21,70) and rs757110 (*ABCC8*) are consistent. Replication in a larger cohort size may be required to rule out any small-to-moderate effects of these variants on obesity and T2D risk in the Mexican–American population. Although we hypothesized that the potential candidate gene *SERPINF1* (PEDF) may have genetic associations with obesity or metabolic traits based on biological function, we did not observe any such associations in this cohort.

Limitations in this study are the relatively small cohort size and lack of gold standard measurements of obesity and insulin resistance such as body fat measurements and euglycemic-hyperinsulinemic clamp measurements. The age of the subjects may possibly be another limitation of this study because we sampled a significantly younger, healthier population, whereas the onset of T2D is typically at older ages. On the other hand, such a cohort may be useful to identify inherent genetic risks for obesity or diabetes before environmental influences play a significant role in the onset of these diseases. In summary, we report the lack of genetic association between rs846910 (*HSD11B1*), rs1205 (*CRP*), rs1501299 (*ADIPOQ*), rs1801282 (*PPARG*), rs757110 (*ABCC8*), and rs1136287 (*SERPINF1*) and obesity and metabolic quantitative traits in a young Mexican American population from south Texas. Lack of associations with these SNPs does not necessarily rule out the six genes as potential obesity candidate genes. We report, for the first time, a possible association between rs1800497 and central obesity in this population.

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Table 1

Examples of previous association studies of the investigated candidate gene SNPs, with obesity and/or obesity-related phenotypes

Gene/SNP	First author/Year/Reference	Ethnic group	*n*	Phenotype	*p*
HSD11B1 rs846910*	Nair 2004 (26)	Pima Indian	706	T2D	0.01
		Pima Indian	127	Insulin sensitivity	0.03
CRP rs1205*	Eiriksdottir 2009 (24	Caucasian (Icelandic)	2130	BMI	0.045
ADIPOQ rs1501299	Sutton 2005 (70)	Hispanic	811	BMI, WC	*NS*
	Siitonen 2011 (23)	Caucasian (Finnish)	507	Body weight	0.02
	Richardson 2006 (21)	Mexican-American	439	Obesity, T2D, HOMA-IR	*NS*
PPARG rs1801282	Fornage 2005 (53)	Caucasian	1954	BMI, WC	0.01, 0.01
	Cole 2000 (17)	Mexican-American	921	BMI, WC	0.015, 0.028
	Hsueh 2001 (19)	Mexican-American	453	Obesity	0.03
	Canizales-Quinteros 2007 (16)	Mexican-Mestizo	131	Obesity	0.007
ABCC8 rs757110*	Florez 2004 (65)	Caucasians, Asians, African Americans	>3400	T2D	0.02
SERPINF1 rs1136287*	Hiroyuki 2007 (22)	Japanese	416	Diabetic retinopathy	*NS*
ANKK1 rs1800497	Noble 1994 (29)	Non-Hispanic and Hispanic	73	Obesity	<0.002
	Spitz 2000 (71)	Caucasian	176	Obesity BMI	0.002
	Thomas 2001 (30)	Chinese	990	Obesity BMI, WC	0.02

n = subjects included in the study.

NS, not significant; BMI, body mass index; WC, waist circumference; T2D, type 2 diabetes, HOMA-IR, homeostasis model assessment of insulin resistance.

*SNPs not investigated in Hispanic cohorts to date.

Table 2

Anthropometric and clinical characteristics of the study group

Characteristics	Median	±SD	Interquartile	Min	Max
M/F	155/293				
Age (Years)	16	±3.53	15–19	14	30
BMI (kg/m2)					
General	24.69	±6.28	21.86–29.06	15.67	52.21
Females	24.25	±6.29	21.86–29.05	17.17	52.21
Males	25.4	±6.25	21.98–29.46	15.67	47.65
WC (cm)					
General	82	±16.26	74.92–94	30	157
Women	81	±14.79	74–92	40.5	128.73
Men	83.35	±18.62	76–97	30	157
SBP (mmHg)	110	±11.25	100–118	85	156
DBP (mmHg)	69	±8.89	62–74	43	97
Fasting plasma glucose (mmol/l)	85 *a*	±17.76	79.65–93	43	266
LogTG (mmol/l)	1.81 *b*	±0.22	1.6627–1.9530	1.2552	2.6053
HOMA-IR	2.13 *c*	±2.08	1.3252–3.3296	0.1377	19.7481

BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; HOMA-IR, homeostasis model assessment of insulin resistance; Log TG, triglycerides logarithmically transformed.

Number of subjects :

a 239,

b 302,

c 297.

Table 3

Genotype and allele frequencies of the seven analyzed SNPs and Hardy-Weinberg calculations

SNPs (genes)	Major/minor allele	Major allele homozygote (%)	Heterozygote (%)	Minor allele homozygote (%)	MAF	HWE *p*
rs846910 (*HSD11B1*)	G/A	230 (74.3)	80 (23.2)	7 (2.5)	0.14	1.0
rs1205 (*CRP*)	C/T	134 (40.4)	155 (49.5)	28 (10.1)	0.34	0.07826
rs1501299 (*ADIPOQ*)	G/T	207 (64.4)	93 (29.1)	17 (6.4)	0.21	0.1585
rs1801282 (*PPARG*)	C/G	236 (75.3)	73 (22.2)	8 (2.5)	0.13	0.3604
rs1800497 (*ANKK1*)	G/A	120 (38.3)	148 (46.5)	49 (15.2)	0.38	0.8129
rs757110 (*ABCC8*)	A/C	127 (39.5)	153 (49)	37 (11.5)	0.36	0.4631
rs1136287 (*SERPINF1*)	T/C	94 (29.8)	165 (53.5)	58 (16.7)	0.43	0.3638

HWE *p*, Hardy Weinberg calculation; MAF, minor allele frequency.

Table 4

Association of SNPs with obesity (BMI) on top and central obesity (WC) on bottom, adjusted for age and gender

		n	MAF				
SNP (Gene)	**Major/Minor allele**	**Non-obese/Obese**	**Non-obese (BMI)**	**Obese (BMI)**	**OR (95%CI)**	***p***	**Permuted *p***
rs846910 (*HSD11B1*)	G/A	179/98	0.13	0.18	0.8524 (0.3804–1.91)	0.6	0.9
rs1205 (*CRP*)	C/T	186/101	0.33	0.32	0.9546 (0.611–1.491)	0.8	1.0
rs1501299 (*ADIPOQ*)	G/T	181/99	0.20	0.25	1.274 (0.7844–2.07)	0.3	0.9
rs1801282 (*PPARG*)	C/G	184/101	0.13	0.14	1.713 (0.8212–3.573)	0.1	0.6
rs1800497 *(ANKK1)*	G/A	181/106	0.34	0.42	1.47 (1.005–2.15)	0.04	0.2
rs757110 (*ABCC8*)	A/C	179/105	0.37	0.34	0.8108 (0.5356–1.227)	0.3	0.9
rs1136287 (*SERPINF1*)	T/C	178/103	0.44	0.43	0.9356 (0.6428–1.362)	0.7	0.9
SNP (gene)	Major/Minor allele	Non-obese/Centrally obese	Non-obese (WC)	Centrally obese (WC)	OR (95%CI)	*p*	Permuted *p*
rs846910 (*HSD11B1*)	G/A	167/185	0.11	0.16	1.035 (0.527– 2.031)	0.9	1.0
rs1205 (*CRP*)	C/T	174/190	0.34	0.34	1.026 (0.7084–1.487)	0.8	1.0
rs1501299 (*ADIPOQ*)	G/T	170/185	0.21	0.20	1.144 (0.7299–1.793)	0.5	0.9
rs1801282 (*PPARG*)	C/G	173/190	0.12	0.14	1.872 (0.8402–4.172)	0.1	0.5
rs1800497 *(ANKK1)*	G/A	169/197	0.31	0.44	1.54 (1.114–2.129)	0.009	0.03
rs757110 (*ABCC8*)	A/C	168/195	0.37	0.34	0.8375 (0.591–1.187)	0.3	0.9
rs1136287 (*SERPINF1*)	T/C	166/191	0.40	0.45	1.174 (0.851–1.618)	0.3	0.9

n = number of subjects genotyped.

OR, odds ratio; MAF, minor allele frequency.

Table 5

Association of SNPs with quantitative traits adjusted for gender, age and BMI

SNP (Gene)	Genotype	HOMA-IR			Fasting plasma glucose (mmol/l)			Log TG (mmol/l)			SBP (mmHg)			DBP (mmHg)		
		Median (SD)	*p*	Permuted *p*	Median (SD)	*p*	Permuted *p*	Median (SD)	*p*	Permuted *p*	Median (SD)	*p*	Permuted *p*	Median (SD)	*p*	Permuted *p*
rs846910 (*HSD11B1)*	GG	1.682 (2.242)	0.04	0.2	51.9 (46.55)	0.7	0.9	1.231 (0.8783)	0.03	0.2	109.5 (11.09)	0.8	1.0	67.98 (8.765)	0.3	0.9
	GA	1.987 (1.917)			44.17 (45.08)			1.308 (0.8685)			110.7 (11.18)			68.82 (9.098)		
	AA	2.579 (1.691)			64.16 (37.23)			1.783 (0.112)			106.0 (6.585)			68.33 (10.92)		
rs1205 (*CRP)*	CC	1.811 (2.574)			49.25 (44.34)			1.245 (0.8702)			109.7 (11.42)	0.4	0.9	68.07 (8.756)		
	CT	1.619 (1.742)	0.03	0.2	50.87 (44.85)	0.007	0.1	1.216 (0.8881)	0.1	0.5	109.5 (10.69)			68.01 (9.139)	0.1	0.7
	TT	1.944 (2.062)			50.88 (58.3)			1.288 (0.8744)			109.8 (12.38)			69.53 (9.367)		
rs1501299 (*ADIPOQ)*	GG	1.688 (1.818)	0.6	0.9	47.18 (44.24)	0.9	1.0	1.274 (0.8749)	0.5	0.9	109.4 (10.41)	0.2	0.7	67.97 (9.005)	0.9	1.0
	GT	1.889 (2.877)			60.27 (48.63)			1.135 (0.8971)			109.8 (11.8)			68.62 (8.68)		
	TT	1.29 (1.501)			53.67 (44.93)			1.053 (0.949)			114.0 (15.44)			69.18 (9.43)		
rs1801282 (*PPARG)*	CC	1.804 (2.263)			52.84 (45.17)			1.256 (0.8747)			109.5 (10.79)			68.22 (9.197)		
	CG	1.537 (1.74)	0.1	0.7	43.36 (47.51)	0.1	0.5	1.188 (0.888)	0.6	1.0	108.6 (12.02)	0.07	0.3	67.74 (8.488)	0.8	1.0
	GG	1.361 (1.873)			36.0 (54.06)			1.027 (0.9871)			118.6 (11.72)			71.11 (7.849)		
rs1800497 *(ANKK1)*	GG	1.461 (1.701)			52.49 (44.02)			1.146 (0.8863)			109.1 (10.75)			67.04 (7.687)		
	GA	1.903 (2.155)	0.4	0.9	50.4 (47.13)	0.7	0.9	1.29 (0.8614)	0.8	1.0	110.2 (11.85)	0.8	1.0	69.54 (9.395)	0.8	1.0
	AA	2.216 (3.038)			50.41 (47.71)			1.364 (0.8503)			109.9 (10.83)			67.12 (9.648)		
rs757110 (*ABCC8)*	AA	1.688 (1.858)			51.76 (44.09)			1.206 (0.8752)			111.0 (11.1)			68.56 (8.328)		
	AC	1.841 (2.444)	0.7	0.9	53.48 (47.61)	0.7	1.0	1.261 (0.8712)	0.5	0.9	109.6 (11.91)	0.1	0.6	68.22 (9.482)	0.5	0.9
	CC	1.799 (2.021)			37.33 (44.28)			1.234 (0.8992)			106.6 (8.136)			68.24 (8.804)		
rs1136287 (*SERPINF1)*	TT	1.773 (1.784)	0.7	1.0	53.23 (48.54)	0.1	0.4	1.296 (0.8691)	0.5	0.9	110.0 (10.33)	0.4	0.9	68.78 (7.997)	0.2	0.8
	TC	1.873 (2.459)			52.96 (45.22)			1.216 (0.8829)			109.9 (11.34)			68.53 (9.308)		
	CC	1.462 (1.888)			48.46 (43.41)			1.201 (0.87120)			108.8 (11.980			67.05 (8.376)		

SBP, systolic blood pressure; DBP, diastolic blood pressure; HOMA-IR, homeostasis model assessment of insulin resistance; Log TG, triglycerides logarithmically transformed.