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ORIGINAL DATA

Variations in *ADIPOR1* But Not *ADIPOR2* are Associated With Hypertriglyceridemia and Diabetes in an Admixed Latin American Population

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■ Abstract

BACKGROUND: Adiponectin is a hormone secreted by adipose tissue. It regulates glycolysis and lipolysis and is involved in the pathophysiology of diabetes and related disorders. Its activity is mainly mediated by the transmembrane receptors AdipoR1 and AdipoR2, which are encoded by *ADIPOR1 (1q32.1)* and *ADIPOR2 (12p13.33)* genes, respectively. In genetic association studies, single nucleotide polymorphisms (SNPs) in or near these genes have been associated with metabolic alterations. However, these relationships are still controversial. **AIM**: The aim of this work was to analyze possible associations between *ADIPOR1/2* and diabetes and other metabolic disorders. **METHODS**: A genetic association study was carried out in an admixed Latin American population. A sample of 200 adults was analyzed. Clinical and serum-biochemical characteristics were measured to diagnose obesity, abdominal obesity, hypertension, hyperglycemia, hypertriglyceridemia, low HDLc, insulin resistance (HOMA-IR), and diabetes. Three SNPs were genotyped in *ADIPOR1* (rs10494839, rs12733285, and rs2275737) and *ADIPOR2* (rs11061937, rs11612383, and rs2286383). For the association analysis, an additive model was assessed through logistic regression. An admixture adjustment was performed using a Monte-Carlo-Markov-Chain method, assuming a three-hybrid substructure (k = 3). **RESULTS**: Two SNPs in A*DIPOR1* were associated with diabetes: rs10494839 (OR = 3.88, adjusted p < 0.03) and rs12733285 (OR = 4.72, adjusted p < 0.03). Additionally, rs10494839 was associated with hypertriglyceridemia (OR = 2.16, adjusted p < 0.01). None of the SNPs in *ADIPOR2* were associated with metabolic disorders. **CONCLUSIONS**: *ADIPOR1* was consistently associated with diabetes and hypertriglyceridemia. This association was maintained even after adjusting for genetic stratification. There were no significant associations involving *ADIPOR2*.

Keywords: diabetes mellitus · adiponectin · adiponectin receptor · ADIPOR1 · ADIPOR2 · hypertriglyceridemia · genetic association study

1. Introduction

Adiponectin is a 30 kDa collagen-like protein with autocrine, paracrine, and endocrine activity, mainly secreted by adipocytes; it has physiologic effects on insulin sensitivity and energetic homeostasis [1, 2]. Most systemic responses to adiponectin are mediated by two specific transmembrane receptors known as AdipoR1 and AdipoR2, which are members of the progesterone and AdipoQ receptor (PAQR) family. They are abundantly expressed in many cellular types, such as hepatocytes, endothelial cells, myocytes, and neurons, among others [3, 4].

Adiponectin receptors have a seven-transmembrane-domain architecture that confers their ligand recognition function on the extracellular surface; it also has a zinc-binding site and an in-

trinsic ceramidase activity oriented to the intracellular space [3, 5]. The appropriate stimulus triggers conformational changes in the receptor structure that increases the intrinsic enzymatic activity. In muscle cells, this activity enhances the beta-oxidative pathway, glucose capture, and glycolysis, whereas in hepatocytes, these changes reduce gluconeogenesis [6-9]. Other responses have linked AdipoR1/R2 to the satiety cycle in the hypothalamus, NOS-induced vascular relaxation in endothelial cells, and inflammatory cascades in macrophages, among others [10-12].

It has been widely proposed that variations in genes encoding these receptors may be associated with alterations in some biological processes in which the hormone is involved. It has been found that several single nucleotide polymorphisms (SNPs) in *ADIPOR1* (1q32.1) and *ADIPOR2* (12p13.33) are associated with plasma concentrations of adiponectin, abdominal obesity, and related disorders (i.e., insulin resistance, hyperglycemia, and high serum triglycerides, among others) [13-16]. According to these data, both genes have been raised as promising targets of treatment approaches to induce complex metabolic alteration. However, some controversial issues remain based on reports of contradictory evidence where no significant associations were found [17, 18].

The Latin American population has recently been exposed to increased racial admixture. Phenotypic expressions of metabolic traits are highly diverse in this population, and the prevalence of related disorders shows remarkable variation between countries [19, 20]. This diversity is an opportunity to uncover associated genetic factors that might be helpful to solve current discrepancies [21]. On this basis, we conducted a study aiming to describe the relationship between common variations in *ADIPOR1*/*R2* with metabolic disorders and syndromes in a Latin America population.

Abbreviations:

ADIPOR1	adiponectin receptor 1 (gene)
ADIPOR2	adiponectin receptor 2 (gene)
AdipoR1	adiponectin receptor 1
AdipoR2	adiponectin receptor 2
AIM	ancestry informative marker
ANOVA	analysis of variance
BMI	body mass index
F_{is}	Wright's coefficient of inbreeding
GPAQ	Global Physical Activity Questionnaire
HbA1c	glycosylated hemoglobin A1c
HDLc	high-density lipoprotein cholesterol
HOMA-IR	homeostasis model assessment for insulin resistance
IR	interquartile range
JNC8	8th Joint National Committee
MAF	minor allele frequency
NOS	nitric oxide synthase
PAQR	progestin and AdipoQ receptor
qPCR	quantitative polymerase chain reaction
r2	correlation coefficient
SNiPA	single nucleotide polymorphism annotator
SNP	single nucleotide polymorphism
T2DM	type 2 diabetes mellitus
WHO	World Health Organization
Y-STR	Y chromosome short tandem repeats

2. Methods and materials

2.1 Subjects

A cross-sectional study was carried out in Cartagena de Indias, a city of nearly 1 million inhabitants located at the Colombian Caribbean Coast [22]. The genetic stratification of this population has been described elsewhere; it is known to be a three-hybrid admixed population including European (60%), African (30%), and Amerindian (10%) ancestry [23, 24]. A sample of 200 adults was employed to achieve 80% power for discrimination of a genetic association with a 2.5/3.5 (heterozygotes/homozygotes) odds ratio, assuming an outcome with 25% prevalence, 25% minor allele frequency, complete linkage disequilibrium (D' = 1), and 5% alpha-coefficient (for type I error), according to calculations described by other authors. We used the browser program Genetic Power Calculator (http://zzz.bwh.harvard.edu/gpc/cc2.html) [25, 26].

Subjects were selected from the urban zone and only no-sibling adults (18-80 years) were allowed to participate. To identify possible cases of consanguinity, individuals with similar surnames were contacted by telephone to discard family relations. On this basis, first- and second-degree siblings were excluded, retaining only one of the subjects for further analysis. Individuals with a personal history of primary endocrine disorders, genetic disease, or surgical treatment for obesity were excluded. Also, pregnant or breast feeding women were excluded. All subjects were asked to participate, and their written informed consent was obtained, following the Universidad de Cartagena ethics committee recommendations.

Selected subjects were enrolled by a trained physician, and underwent a medical examination focused on sociodemographic variables and clinical history of metabolic disorders. Physical activity and sedentary behavior were noted in the Global

Physical Activity Questionnaire (GPAQ) developed by the World Health Organization (WHO) for physical activity surveillance [27].

2.2 Anthropometric data

Anthropometric parameters (height, weight, and waist circumference,) were measured during physical examination following the international diabetes guidelines for the metabolic syndrome and WHO recommendations [28-30]. Height was measured to the nearest half centimeter using a stadiometer with the participant barefoot, and registered in meters. Weight was measured to the nearest 0.1 kilogram (kg) using a calibrated digital scale, with the subjects wearing light clothes without shoes. Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m^2). Using an inelastic tape measure, waist circumference was measured at two centimeters below the umbilicus with the subjects in a standing position, their weight equally distributed on both feet, arms at their sides, and head facing straight forward at the end of a normal expiration, ensuring that the tape did not compress the skin and was parallel to the floor. Blood pressure was measured using a sphygmomanometer after a resting period of at least 5 min, using the auscultatory method according to recommendations from the 8th Joint National Committee (JNC8) [29].

2.3 Blood samples

A whole-blood sample was collected under 8-hour fasting conditions to measure serum concentrations of glucose, triglycerides, HDL cholesterol (HDLc), insulin, adiponectin, and the proportion of glycosylated hemoglobin (HbA1c). An aliquot blood was stored for further genetic analyses.

2.4 Definition of obesity, hypertension, and the metabolic syndrome

Using the anthropometric parameters and biochemical data, metabolic traits (BMI) were defined following the criteria defined by the WHO:

- Normal weight: BMI 18.51-24.99 kg/m^2
- Overweight: BMI 25-29.99 kg/m^2
- Obesity as BMI ≥ 30 kg/m^2

Body weight excess was determined by the addition of overweight and obesity categories [31].

Hypertension was defined according to the JNC8 [29]:

- Younger than 60 years old: systolic ≥140 mmHg, diastolic ≥90 mmHg
- Adults 60 years old or more: systolic ≥150 mmHg, diastolic ≥90 mmHg.

The metabolic syndrome and its related alterations were defined according to Joint Interim Statement criteria:

1. Abdominal obesity: waist circumference men ≥90 cm, women ≥80 cm.
2. Dyslipidemia: hypertrigliceridemia: TG ≥150 mg/dl (1.7 mmol/l) or drug treatment for high serum triglycerides. Low HDLc: men, HDLc <40 mg/dl (1.0 mmol/l); women, HDLc <50 mg/dl (1.3 mmol/l)).
3. Hyperglycemia: glucose impaired fasting ≥100 mg/dl or drug treatment for elevated glucose [32].

2.5 Definition of insulin resistance

The definition of insulin resistance was based on the homeostasis model assessment for insulin resistance (HOMA-IR), as described by other authors. Subjects in the last quintile were considered to be insulin resistant [33]. The same procedure was applied to determine high serum adiponectin status in the sample population. Type 2 diabetes mellitus (T2DM) was defined by HbA1c ≥ 6.5%, as proposed by the American Diabetes Association, or by a history of the disease [34].

2.6 Genotyping

For genotyping assays prior to molecular procedures, common variants in *ADIPOR1* and *ADIPOR2* were identified using 1000 genome project reports, with the bioinformatic resource *SNiPA* [35, 36]. SNPs with a minor allele frequency (MAF) ≥0.25 and correlation coefficient (r^2) = 1.0 were selected using data from populations with European ancestry (**Tables A1** and **A2**). Among the tagged variants, a set of SNPs in both genes was picked. For *ADIPOR1*, the included variants were:

- rs10494839 (proxy for rs75114693, rs10920533, rs10920534, rs10920537, rs6666089, and rs2232853)
- rs12733285
- rs2275737 (proxy for rs2275736, rs2275738, and rs7514221)

Table 1. Allelic frequencies and genotype distributions for *ADIPOR1* and *ADIPOR2* genes

Gene	n (%)	F_{is}	p
ADIPOR1			
rs10494839			
C	87 (21.9)	0.023	0.56
T	311 (78.1)		
CC	10 (5.0)		
CT	67 (33.7)		
TT	122 (61.3)		
rs12733285			
C	309 (77.6)	0.026	0.56
T	89 (22.4)		
CC	121 (60.8)		
CT	67 (33.7)		
TT	11 (5.5)		
rs12733285			
A	159 (39.9)	0.112	0.25
C	239 (60.1)		
AA	37 (18.6)		
AC	85 (42.7)		
CC	77 (38.7)		
ADIPOR2			
rs12733285			
A	159 (39.9)	0.112	0.25
C	239 (60.1)		
AA	37 (18.6)		
AC	85 (42.7)		
CC	77 (38.7)		
rs12733285			
A	159 (39.9)	0.112	0.25
C	239 (60.1)		
AA	37 (18.6)		
AC	85 (42.7)		
CC	77 (38.7)		
rs12733285			
A	159 (39.9)	0.112	0.25
C	239 (60.1)		
AA	37 (18.6)		
AC	85 (42.7)		
CC	77 (38.7)		

Similarly, for *ADIPOR2* the variants were:

- rs11061937 (proxy for rs11061919, rs11061923, 10773986, 7975826)
- rs11612383
- rs2286383 (proxy for rs9805049, rs2286384)

These SNPs are proxy markers for several variants identified through datasets from the 1000 genome project; they include positive antecedents of genetic association with metabolic traits and related diseases identified previously [37-41].

Selected SNPs were genotyped with quantitative polymerase chain reaction (qPCR) using specific TaqMan probes (Thermo Fisher Scientific, Inc., Waltham, MA, USA). Allelic discrimination was performed automatically with endpoint fluorescent data, which were analyzed using StepOne Real-Time PCR Software (Thermo Fisher Scientific, Inc., Waltham, MA, USA).

2.7 Statistics

For statistical procedures, sociodemographic data, personal and family antecedents, as well as anthropometric measures and serum concentrations were described using main tendency and frequency values. When appropriate, mean values were compared using Student's *t*-test, and frequencies were compared with X^2 or Fisher's exact tests.

Allelic and genotypic frequencies were determined by direct count, linkage disequilibrium was estimated employing Arlequin 3.5 [42], and Hardy-Weinberg Equilibrium was assessed through F_{is} values using Genetix 4.05 software. Given that *ADIPOR1* and *ADIPOR2* represent distant loci, genetic associations were analyzed separately. Associations between continuous traits and genotype distributions were analyzed using the Kruskal-Wallis test and analysis of variance (ANOVA). Relations between categorical outcomes (i.e., hypertension or T2DM) and genotypes were determined with X^2 tests. In both cases, recessive and dominant models were assessed using null hypothesis tests [43]. Additive models for genotype-phenotype associations were evaluated through logistic regression, where risk alleles were equal to the unit (risk allele = 1), and anthropometric alterations and metabolic disorders were interpreted as categorical outcomes. Logistic regression was adjusted by age, sex, and BMI, except for body weight excess (overweight and obesity) analysis, for which only age and sex were used. These procedures were performed with R version 3.2.1 and the package PredictABEL 1.2-2 [44, 45]. Based on Bonferroni's correction for multiple testing, p-values <0.017 were considered as statistically significant.

Associations were adjusted by genetic stratification assuming a three-hybrid substructure (k = 3) using a Bayesian approach (Markov Chain Monte Carlo, or MCMC) with 100,000 replications using the STRAT software version 1.1 for DOS/Windows [46].

Table 2. Genotype distributions for *ADIPOR1* single nucleotide polymorphisms according to metabolic traits

Anthropometric and biochemical parameters	rs10494839						rs12733285						rs2275737					
	CC	CT	TT	p*			TT	TC	CC	p*			AA	AC	CC	p*		
					TT vs. CT+ CC	CC vs. CT+ TT				CC vs. CT+ TT	TT vs. CC+ CT					CC vs. AC+ AA	AA vs. AC+ CC	
BMI																		
Normal weight	1(10.0)	36(53.7)	66(54.1)				5(45.5)	38(56.7)	60(49.6)				19(51.4)	46(54.1)	38(49.4)			
Overweight	7(70.0)	23(34.3)	40(32.8)				3(27.3)	20(29.9)	47(38.8)				13(35.1)	28(32.9)	29(37.7)			
Obese	2(20.0)	8(11.9)	16(13.1)	0.105	0.655	0.022*	3(27.3)	9(13.4)	14(11.6)	0.459	0.369	0.350	5(13.5)	11(12.9)	10(13.0)	0.978	0.834	0.995
WC																		
Abd. obesity	8(80.0)	41(61.2)	71(58.2)				8(72.7)	40(59.7)	72(59.5)				18(48.6)	52(61.2)	50(64.9)			
Not altered	2(20.0)	26(38.8)	51(41.8)	0.392	0.538	0.329	3(27.3)	27(40.3)	49(40.5)	0.686	0.890	0.582	19(51.4)	33(38.8)	27(35.1)	0.244	0.361	0.155
BP																		
Hypertension	3(30.0)	14(20.9)	31(25.4)				4(36.4)	19(28.4)	25(20.7)				8(21.6)	16(18.8)	24(31.2)			
Not altered	7(70.0)	53(79.1)	91(74.6)	0.711	0.715	0.946	7(63.6)	48(71.6)	96(79.3)	0.308	0.210	0.539	29(78.4)	69(81.2)	53(68.8)	0.172	0.093	0.856
Serum glucose																		
Hyperglycemia	1(10.0)	12(17.9)	22(18.0)				0(0.0)	14(20.9)	21(17.4)				4(10.8)	14(16.5)	17(22.1)			
Not altered	9(90.0)	55(82.1)	100(82.0)	0.811	0.987	0.825	11(100)	53(79.1)	100(82.6)	0.239	0.99	0.242	33(89.2)	71(83.5)	60(77.9)	0.314	0.258	0.336
Serum TG																		
HyperTG	8(80.0)	47(70.1)	108(88.5)				11(100)	55(82.1)	97(80.2)				33(89.2)	69(81.2)	61(79.2)			
Not altered	2(20.0)	20(29.9)	14(11.5)	0.007*	0.004*	0.99	0(0.0)	12(17.9)	24(19.8)	0.261	0.543	0.229	4(10.8)	16(18.8)	16(20.8)	0.421	0.552	0.299
Serum HDLc																		
Low HDLc	1(10.0)	21(31.3)	43(35.2)				5(45.5)	24(35.8)	36(29. 8)				16(43.2)	29(34.1)	20(26.0)			
Not altered	9(90.0)	46(68.7)	79(64.8)	0.251	0.410	0.221	6(54.5)	43(64.2)	85(70.2)	0.452	0.349	0.548	21(56.8)	56(65.9)	57(74.0)	0.171	0.148	0.184
MetS																		
Yes	3(30.0)	24(35.8)	49(40.2)				5(45.5)	25(37.3)	46(38.0)				11(29.7)	31(36.5)	34(44.2)			
No	7(70.0)	43(64.2)	73(59.8)	0.724	0.567	0.831	6(54.5)	42(62.7)	75(62.0)	0.874	0.99	0.848	26(70.3)	54(63.5)	43(55.8)	0.302	0.220	0.323
Insulin resistance																		
Yes	0(0.0)	4 (6.0)	7(5.7)				0(0.0)	4(6.0)	7(5.8)				3(8.1)	4(4.7)	4 (5.2)			
No	10(100.0)	63(94.0)	115(94.3)	0.733	0.99	0.940	11(100)	63(94.0)	114(94.2)	0.710	0.99	0.883	34(91.9)	81(95.3)	73(94.8)	0.741	0.99	0.716
Diabetes																		
Yes	1(10.0)	4 (6.0)	19(15.6)				0(0.0)	4(6.0)	20(16.5)				3(8.1)	6(7.1)	15(19.5)			
No	9(90.0)	63(94.0)	103(84.4)	0.149	0.073	0.991	11(100)	63(94.0)	101(83.5)	0.046*	0.028*	0.431	34(91.9)	79(92.9)	62(80.5)	0.037*	0.019*	0.590
High serum adiponectin																		
Yes	0(0.0)	2(3.0)	8(6.6)				0(0.0)	3(4.5)	7(5.8)				0(0.0)	5(5.9)	5 (6.5)			
No	10(100.0)	65(97.0)	114(93.4)	0.424	0.3616	0.997	11(100)	64(95.5)	114(94.2)	0.680	0.780	0.940	37(100.0)	80(94.1)	72(93.5)	0.295	0.674	0.256

Legend: Data are numbers (%). * $p < 0.05$, *Abbreviations*: Abd. obesity - abdominal obesity, BMI - body mass index, HDLc - high-density lipoprotein cholesterol, HyperTG - hypertriglyceridemia, MetS - metabolic syndrome, TG - triglycerides, WC - waist cricumference.

2.8 Admixture pattern

The three-hybrid admixture pattern applied is based on previous reports from Cartagena de Indias, where ancestry informative markers (AIMs) and the Y chromosome were used to describe local genetic substructure and ancestry distribution [23, 24, 47, 48]. In this study, a total of 17 Y chromosome short tandem repeats (Y-STR; AmpFLSTR® Yfiler® PCR Amplification Kit, Thermo Fisher, Inc., USA) were used to confirm the admixture in sampled males (data not shown).

3. Results

3.1 Age, income, and physical activity – descriptive data

A total of 200 subjects were included in the study (44.5% men and 55.5% women), with an average age of 33.7 ± 14.2 years. Age ranges were distributed according to a population pyramid [49]:

1. 18-29 years = 53.8%

Table 3. Genotype distributions for *ADIPOR2* single nucleotide polymorphisms according to metabolic traits

Anthropometric and biochemical parameters	rs11061937						rs11612383						rs2286383					
	CC	CT	TT	p*	TT vs. CT+TT	CC vs. CT+TT	TT	TC	CC	p*	GG vs. AG+AA	AA vs. AG+GG	AA	AC	CC	p*	GG vs. AG+AA	AA vs. AG+GG
BMI																		
Normal weight	16(53.3)	49(50.0)	38(53.5)				8(44.4)	58(58.6)	37(45.1)				7(36.8)	57(54.8)	39(51.3)			
Overweight	9(30.0)	34(34.7)	27(38.0)				9(50.0)	29(29.3)	32(39.0)				9(47.4)	34(32.7)	27(35.5)			
Obese	5(16.7)	15(15.3)	6 (8.5)	0.672	0.346	0.727	1 (5.6)	12(12.1)	13(15.9)	0.235	0.272	0.317	3(15.8)	13(12.5)	10(13.2)	0.712	0.995	0.384
WC																		
Abd. obesity	15(50.0)	63(64.3)	42(59.2)				9(50.0)	61(61.6)	50(61.0)				14(73.7)	65(62.5)	41(53.9)			
Not altered	15(50.0)	35(35.7)	29(40.8)	0.364	0.924	0.142	9(50.0)	38(38.4)	32(39.0)	0.642	0.987	0.493	5(26.3)	39(37.5)	35(46.1)	0.233	0.196	0.313
BP																		
Hypertension	4(13.3)	25(25.5)	19(26.8)				3(16.7)	24(24.2)	21(25.6)				9(47.4)	24(23.1)	15(19.7)			
Not altered	26(86.7)	73(74.5)	52(73.2)	0.319	0.223	0.205	15(83.3)	75(75.8)	61(74.4)	0.723	0.808	0.626	10(52.6)	80(76.9)	61(80.3)	0.039*	0.334	0.027
Serum glucose																		
Hyperglycemia	3(10.0)	18(18.4)	14(19.7)				2(11.1)	20(20.2)	13(15.9)				4(21.1)	21(20.2)	10(13.2)			
Not altered	27(90.0)	80(81.6)	57(80.3)	0.483	0.693	0.355	16(88.9)	79(79.8)	69(84.1)	0.560	0.727	0.665	15(78.9)	83(79.8)	66(86.8)	0.433	0.271	0.920
Serum TG																		
HyperTG	24(80.0)	81(82.7)	58(81.7)				15(83.3)	79(79.8)	69(84.1)				16(84.2)	89(85.6)	58(76.3)			
Not altered	6(20.0)	17(17.3)	13(18.3)	0.945	0.990	0.970	3(16.7)	20(20.2)	13(15.9)	0.741	0.617	0.990	3(15.8)	15(14.4)	18(23.7)	0.270	0.155	0.99
Serum HDLc																		
Low HDLc	9(30.0)	35(35.7)	21(29.6)				6(33.3)	33(33.3)	26(31.7)				7(36.8)	29(27.9)	29(38.2)			
Not altered	21(70.0)	63(64.3)	50(70.4)	0.664	0.593	0.899	12(66.7)	66(66.7)	56(68.3)	0.971	0.930	0.990	12(63.2)	75(72.1)	47(61.8)	0.320	0.252	0.879
MetS																		
Yes	9(30.0)	41(41.8)	26(36.6)				6(33.3)	39(39.4)	31(37.8)				12(63.2)	38(36.5)	26(34.2)			
No	21(70.0)	57(58.2)	45(63.4)	0.477	0.851	0.424	12(66.7)	60(60.6)	51(62.2)	0.884	0.99	0.849	7(36.8)	66(63.5)	50(65.8)	0.059	0.448	0.035*
Insulin resistance																		
Yes	4(13.3)	4 (4.1)	3 (4.2)				1 (5.6)	6 (6.1)	4 (4.9)				1 (5.3)	4 (3.8)	6 (7.9)			
No	26(86.7)	94(95.9)	68(95.8)	0.127	0.783	0.110	17(94.4)	93(93.9)	78 (95.1)	0.941	0.983	0.99	18(94.7)	100(96.2)	70(92.1)	0.501	0.406	0.99
Diabetes																		
Yes	1(3.3)	14(14.3)	9(12.7)				0(0)	13(13.1)	11(13.4)				5(26.3)	13(12.5)	6 (7.9)			
No	29(96.7)	84(85.7)	62(87.3)	0.267	0.990	0.197	18(100)	86(86.9)	71(86.6)	0.257	0.787	0.204	14(73.7)	91(87.5)	70(92.1)	0.086	0.232	0.101
High serum adiponectin																		
Yes	3(10.0)	5 (5.1)	2 (2.8)				1 (5.6)	4 (4.0)	5 (6.1)				1 (5.3)	5 (4.8)	4 (5.3)			
No	27(90.0)	93(94.9)	69(97.2)	0.319	0.469	0.368	17(94.4)	95(96.0)	77 (93.9)	0.814	0.802	0.990	18(94.7)	99(95.2)	72(94.7)	0.989	0.99	0.99

Legend: Data are numbers (%). * $p < 0.05$, *Abbreviations*: Abd. obesity - abdominal obesity, BMI - body mass index, HDLc - high-density lipoprotein cholesterol, HyperTG - hypertriglyceridemia, MetS - metabolic syndrome, TG - triglycerides, WC - waist cricumference.

2. 30-39 years = 17.1%
3. 40-49 years = 13.6%
4. 50-59 years = 10.6%
5. 60-69 years = 2.5%
6. 70 or more years = 2.5%

Given that economic status is highly correlated with nutritional conditions, total family income was registered for all subjects. The median income was US$ 364 per month interquartile range (IR, $241-$690).

Sedentary behavior was the most common pattern identified among sampled subjects, with 540 min/day IR (360-720) of low energy-expenditure activities as a median tendency. Mild-intensity activities were regularly executed by 38 (19%) subjects with a median of 60 min/day IR (30-120), and 40 (20%) subjects were found to perform high-intensity activities on a weekly basis with a median of 60 min/day IR (56-120).

3.2 Anthropometric data and diabetes incidence

Regarding anthropometric parameters, median values for weight, height, and BMI were 68.7 kg IR

Table 4. Association of *ADIPOR1* gene variants with metabolic disorders

Metabolic traits	rs10494839					rs12733285					rs2275737				
	Beta-coefficient	OR	95% CI	p*	Adjusted p†	Beta-coefficient	OR	95% CI	p*	Adjusted p†	Beta-coefficient	OR	95% CI	p*	Adjusted p†
Weight excess	-0.355	0.70	0.41-1.20	0.192	0.11	0.169	1.19	0.69-2.05	0.542	0.84	-0.202	0.817	0.52-1.29	0.383	0.67
Abd. obesity	0.018	1.02	0.53-1.94	0.954	0.44	-0.321	0.72	0.38-1.38	0.328	0.83	0.376	1.46	0.84-2.51	0.175	0.24
Hypertension	0.749	2.12	0.95-4.70	0.065	0.36	-0.738	0.48	0.20-1.12	0.089	0.9	0.6475	1.911	0.90-4.06	0.092	0.9
Hyperglycemia	0.448	1.57	0.78-3.13	0.205	0.51	0.094	1.10	0.53-2.28	0.800	0.96	0.389	1.48	0.79-2.74	0.217	0.11
HyperTG	0.770	2.16	1.16-4.07	0.017*	0.01	-0.209	0.81	0.39-1.71	0.581	0.21	-0.049	0.95	0.53-1.72	0.871	0.17
Low HDLc	0.250	1.28	0.64-2.59	0.483	0.24	-0.213	0.81	0.39-1.68	0.567	0.4	-0.456	0.63	0.35-1.16	0.139	0.18
MetS	0.627	1.87	1.01-3.48	0.046	0.05	-0.047	0.95	0.50-1.81	0.884	0.9	0.441	1.55	0.90-2.70	0.117	0.9
Insulin resistance	0.211	1.23	0.40-3.86	0.716	0.81	0.465	1.59	0.49-5.14	0.436	0.52	-0.264	0.78	0.32-1.87	0.560	0.74
Diabetes	1.354	3.88	1.36 -11.06	0.011*	0.03	1.551	4.72	1.37-16.26	0.013*	0.03	0.353	1.42	0.67-3.04	0.359	0.06
High SA	1.147	3.15	0.74-13.44	0.121	0.07	0.339	1.40	0.36-5.54	0.629	0.57	0.826	2.28	0.73-7.12	0.154	0.28

Legend: *p < 0.017 were considered as statistically significant (Bonferroni correction). † Admixture adjustment with Monte-Carlo-Markov Chain (k = 3). An additive model was assessed through a logistic regression where risk alleles were interpreted as the unit. Genetic variations in rs10494839 (CC = 0, CT = 1, and TT = 2), rs12733285 (TT = 0, CT = 1, and CC = 2), and rs2275737 (AA = 0, AC = 1, and CC = 2) were included as independent variables. Age, sex, and body mass index were included as confounding variables (except for the analysis of body weight excess in which only age and sex were used). An admixture adjustment was performed through a Monte-Carlo-Markov Chain where a three-hybrid genetic stratification was assumed. *Abbreviations*: Abd. obesity - abdominal obesity, HDLc - high-density lipoprotein cholesterol, HyperTG - hypertriglyceridemia, MetS - metabolic syndrome, SA - serum adiponectin.

(56.85-78.45), 165 cm (158.3-172), and 24.9 kg/m^2 (21.9-27.68), respectively. The mean value for waist circumference was 88.1 ± 13.5 cm. The median values for blood pressure were 110 mmHg IR (100-118) (systolic) and 88.0 mmHg IR (79.85-97.38) (diastolic). Serum concentration of glucose was 90.0 mg/dl IR (86-96) (5.0 mmol/liter IR (4.8-5.3)), triglycerides 173.0 mmol/l IR (156-192) (2.0 mmol/l IR (1.8-2.2)), HDLc 48.0 mg/dl IR (45-51) (1.2 mmol/l IR (1.2-1.3)), insulin 10 µUI/ml (10-11.65) (71.8 mmol/l IR (71.8-83.6)), and adiponectin 15.5 ng/ml IR (12.5-18-95). The average proportion of HbA1c was 5.0% IR (4.2-6.0). The mean value of HOMA-IR was estimated 2.3 IR (2.1-3.0).

Overweight and obesity were identified in 48.2% and abdominal obesity in 65.3% of individuals. The frequency of hypertension was 24.1%, whereas hyperglycemia, hypertriglyceridemia, and low HDLc were found in 19.1%, 81.9%, and 37.7%, respectively. According to personal antecedents and HbA1C values, T2DM was present in 4% of the sampled subjects. The metabolic syndrome was diagnosed in 85 (42.7%) subjects, and among these, five criteria were met by 5 subjects (2.5%), four by 21 (10.6%), and three by 59 (29.6%).

3.3 Genotyping

Genotyping assays were possible for 199 subjects. In the *ADIPOR1* gene:

- rs10494839 showed an MAF (C allele) of 21.9% (n = 87)
- rs12733285 MAF (T allele) was 22.4% (n = 89)
- rs2275737 MAF (A allele) was 39.9% (n = 159)

In *ADIPOR2*, the MAF for the three assessed SNPs were:

- rs11061937 (C allele) 39.7% (n = 158)
- rs11612383 (A allele) 33.9% (n = 135)
- rs2286383 (A allele) 35.7% (n = 142)

Genotype distributions and F_{is} values for Hardy-Weinberg equilibrium are shown in **Table 1**.

3.4 Genetic associations of continuous anthropometric and metabolic variables

Median and mean values of anthropometric and metabolic variables were compared according to genotype distributions. In *ADIPOR1*, no differences were found when the rs12733285 and rs2275737 genotypes were applied as classification criteria. However, differences in BMI among the three genotypes were found in rs10494839 ($p < 0.02$). Also, the TT+CT group had lower BMI ($p < 0.01$), lower waist circumference ($p < 0.05$), and lower HDLc ($p < 0.05$) than the CC homozygotes;

Table 5. Association of *ADIPOR2* gene variants with metabolic disorders

Metabolic traits	rs11061937					rs11612383					rs2286383				
	Beta-coefficient	OR	95% CI	p*	Adjusted p†	Beta-coefficient	OR	95% CI	p*	Adjusted p†	Beta-coefficient	OR	95% CI	p*	Adjusted p†
Weight excess	0.172	1.19	0.72-1.96	0.499	0.57	-0.173	0.84	0.51-1.40	0.505	0.64	0.091	1.10	0.60-1.99	0.764	0.81
Abd. obesity	0.090	1.10	0.61-1.96	0.759	0.90	0.013	1.01	0.56-1.85	0.965	0.33	0.358	1.43	0.71-2.90	0.319	0.21
Hypertension	-0.125	0.88	0.41-1.91	0.750	0.47	0.146	1.16	0.55-2.43	0.699	0.76	0.579	1.79	0.75-4.25	0.190	0.12
Hyperglycemia	-0.130	0.88	0.45-1.72	0.703	0.40	0.184	1.20	0.62-2.33	0.582	0.86	0.226	1.25	0.60-2.64	0.550	0.32
HyperTG	0.177	1.19	0.65-2.21	0.572	0.80	0.139	1.15	0.61-2.17	0.666	0.66	0.555	1.74	0.83-3.68	0.145	0.28
Low HDLc	-0.201	0.82	0.42-1.60	0.557	0.84	-0.410	0.66	0.34-1.30	0.232	0.96	-0.573	0.56	0.26-1.21	0.142	0.86
MetS	0.138	1.15	0.63-2.10	0.648	0.34	0.182	1.20	0.66-2.20	0.553	0.91	0.554	1.74	0.87-3.47	0.116	0.14
Insulin resistance	0.549	1.73	0.59-5.05	0.314	0.28	0.013	1.01	0.37-2.78	0.979	0.51	-0.162	0.85	0.23-3.10	0.805	0.42
Diabetes	0.006	1.01	0.42-2.39	0.988	0.35	-0.268	0.76	0.34-1.74	0.522	0.13	0.415	1.52	0.61-3.75	0.367	0.20
High SA	0.894	2.45	0.72-8.31	0.151	0.40	-0.138	0.87	0.28-2.68	0.809	0.71	0.459	1.58	0.40-6.31	0.515	0.63

Legend: *p < 0.017 were considered as statistically significant (Bonferroni correction). † Admixture adjustment with Monte-Carlo-Markov Chain (k = 3). An additive model was assessed through a logistic regression where risk alleles were interpreted as the unit. Genetic variations in rs11061937 (TT = 0, CT = 1, and CC = 2), rs11612383 (GG = 0, AG = 1, and AA = 2), and rs2286383 (GG = 0, AG = 1, and AA = 2) were included as independent variables. Age, sex, and body mass index were included as confounding variables (except for the analysis of body weight excess in which only age and sex were used). An admixture adjustment was performed through a Monte-Carlo-Markov Chain where a three-hybrid genetic stratification was assumed. *Abbreviations*: Abd. obesity - abdominal obesity, HDLc - high-density lipoprotein cholesterol, HyperTG - hypertriglyceridemia, MetS - metabolic syndrome, SA - serum adiponectin.

CC+CT genotypes had lower glucose values than TT homozygotes (p < 0.03; **Table A3**). Similarly, in rs12733285, TT homozygotes had higher triglyceride concentrations than CC homozygotes, CT heterozygotes (p < 0.03), and CC+CT genotypes (p < 0.01). In rs2275737, the CC+AC group had a lower triglyceride value than AA homozygotes, and there were differences in mean HDLc and adiponectin levels between the three genotypes (p < 0.03; **Table A3**).

Furthermore, AA+AC genotypes had lower HDLc levels than CC homozygotes (p < 0.01), CC+AC genotypes had higher levels of adiponectin than AA homozygotes (p < 0.01), and AA+AC genotypes had lower levels of adiponectin than CC homozygotes (**Table A3**). For *ADIPOR2*, the AA+AG group had lower values for waist circumference than GG homozygotes in rs11612383 (p < 0.04). Additionally, differences in waist circumference and insulin values between rs2286383 genotypes were found (p < 0.05; **Table A4**).

3.5 Genetic associations of metabolic disorders

We also compared the frequencies of anthropometric parameters with metabolic disorders. We found differences for *ADIPOR1* among cases for high serum triglycerides, with differences in the genotype distribution for rs10494839 (p < 0.01). A recessive model showed a higher occurrence of hypertriglyceridemia in TT homozygotes for rs10494839 when compared with CC+CT genotypes (p < 0.01) (**Table 2**). Similarly, T2DM cases were more frequent among CC homozygotes for rs12733285 (p < 0.05) and for rs2275737 (p < 0.05). These observations were corroborated by a recessive model (**Table 2**). In *ADIPOR2*, high blood pressure was more frequent in subjects with the AA genotype for rs2286383 (p < 0.05), and the metabolic syndrome was less frequent among AA homozygotes (p < 0.04; **Table 3**).

The assessment of an additive model revealed significant associations between rs10494839 (*ADIPOR1*), high serum triglycerides (OR = 2.16, p = 0.01) and T2DM (OR = 3.88, p = 0.01), in which the T allele was identified as a risk factor. The statistical significance of these relationships persisted after admixture adjustment for a three-hybrid population (p = 0.03). Moreover, rs12733285 (*ADIPOR1*) was found to be associated with an increased risk of T2DM (OR = 4.72, p = 0.01). This finding remained statistically significant when the admixture adjustment was applied (p = 0.03; **Table 4**). None of the SNPs analyzed in *ADIPOR2* was associated with any of the metabolic traits included in this study (**Table 5**).

4. Discussion and conclusions

In admixed populations, understanding the genotype/phenotype interactions behind complex diseases remains a challenging task because genetic stratification is a source of false positives caused by confounding phenomena [50]. Therefore,

appropriate analysis requires the application of rigorous ancestry-adjusted statistical procedures, and high-powered methodological designs are often needed to uncover common associations [46, 50]. Despite this challenge, in the present study we found consistent evidence for associations between *ADIPOR1* with high serum triglycerides and T2DM in a Latin American population, where a three-hybrid substructure has been previously reported [23, 24, 47, 48].

The SNPs rs10494839 and rs12733285, located in *ADIPOR1*, were found to be associated with T2DM, which represents an important finding of the present research, considering that this relationship has often been elusive in genetic association studies. According to Bermudez *et al.* (2013), there is little evidence describing an association between *ADIPOR1/2* and T2DM in human populations [51]. In fact, Peters *et al.* (2013) found that *ADIPOQ* but not *ADIPOR1/2* was associated with T2DM, and Kim *et al.* (2009) reported a lack of significant associations of *ADIPOR1/2* genes with this disease [18, 52]. On the other hand, Mather *et al.* (2012) found two SNPs (rs1342387 and rs12733285) in *ADIPOR1* to be significantly associated with diabetes incidence [41], which strongly supports the results of the current study. Similarly, Jin *et al.* (2014) found an association between two SNPs in *ADIPOR1* (rs3737884 and rs16850797) and T2DM in a Chinese population [53], and recently another study successfully replicated these findings with subjects from Northeastern China. Moreover, a third SNP (rs7514221) in *ADIPOR1* was also found to be associated with an increased risk of T2DM [54].

Adiponectin receptors have been widely reported to be involved in the development of T2DM, in both *in vitro* and *in vivo* studies, where the regulatory activity of adiponectin signaling controlling beta-oxidative and glycolytic pathways has been demonstrated [6, 55]. In human populations, variations in the physiologic response to adiponectin have been related to insulin resistance and T2DM. Therefore, both ligand and receptor are thought to be promising targets for novel therapeutics [56]. In this regard, an agonist of adiponectin receptors (AdipoRon) has been reported to ameliorate T2DM in rodents [57], and recently, it was suggested that most of its pharmacological effects are mediated through AdipoR1, although details of intracellular signaling triggered by this molecule remain unclear [58]. In this connection, our results encourage analyses of possible effects of genetic variations in *ADIPOR1* on receptor expression and cellular responses in relation to available agonists because a pharmaco-genomic interaction would be an interfering factor for novel therapies.

Insulin resistance has been described as an early stage in the pathogenesis of glucose intolerance and T2DM [59]. Therefore, we assessed a possible relationship between *ADIPOR1/2* variations, serum insulin concentrations, and HOMA-IR in the present study. Despite the cumulative biologic and epidemiologic evidence regarding this relationship, none of the analyzed SNPs was associated with insulinemia, HOMA-IR values, or insulin resistance. Other authors have obtained similar results, reporting that no genotype/phenotype associations were found when a set of SNPs covering adiponectin receptors genes were analyzed [18]. Rasmussen-Torvik *et al.* (2009) genotyped the same three variations in *ADIPOR1* that were selected in the present work (rs10494839, rs12733285, and rs2275737), and they found no significant relationship with insulin resistance. However, in that study, another SNP in *ADIPOR1* (rs1342387) was associated with an increased diabetes risk [60]. It is well known that adiponectin activity progressively decays, while conversely, serum concentrations of adiponectin increase during the transition from insulin-resistance to T2DM, until a so-called “adiponectin-resistance” status is reached [61, 62]. It is therefore possible that groups with altered responses to insulin represent a diverse population of subjects with different levels of adiponectin activity, which may attenuate the effects of genetic variations on receptor function, causing a confounding scenario for association analysis.

Hypertriglyceridemia was found to be associated with the SNP rs10494839 (*ADIPOR1*) both in the regression model and the MCMC (**Table 6**). To the best of our knowledge, there is scarce evidence regarding this genotype/phenotype relationship, and there have been no previous reports where this particular SNP has been found to be involved as a risk factor for high serum triglycerides. The closest precedents were published by Jin *et al.* (2014) who found that rs16850797 and rs3737884 SNPs in *ADIPOR1* were associated with higher triglyceride levels in subjects with T2DM and coronary artery disease [53], and by Potapov *et al.* (2008) who also found higher serum triglyceride concentrations related to rs2275738 (*ADIPOR1*) among subjects with T2DM, but not in the control group [40]. In contrast, Ferguson *et al.* (2010) genotyped three *ADIPOR1* SNPs (rs2275737, rs10753929, and rs10920533), and found that none of them were related to serum levels of triacylglyc-

erol. In a study carried out with Finnish and Swedish adults, the SNP rs6666089 in *ADIPOR1* also had no association with triacylglycerol levels [63]. Additionally, Yeh *et al*. (2008) found no association between *ADIPOR1* and serum triglycerides in a multi-ethnic Brazilian sample where two variants in regulatory regions were genotyped, which represents one of the most relevant antecedents for South American populations [64].

To date, most findings have pointed to *ADIPOR2* variants as a genetic factor related to high serum triglycerides. Richardson *et al*. (2006) found 14 variants in *ADIPOR2*, but none in *ADIPOR1*, related to serum triglycerides in a study where 6 SNPs in *ADIPOR1* and 24 SNPs in *ADIPOR2* were analyzed [65]. Moreover, Broedl *et al*. (2006) found a cluster of three SNPs in *ADIPOR2* that were related to lower levels of triglycerides in a population sample of European ancestry [16], and Potapov *et al*. (2008) found that TT homozygotes in rs11061971 (*ADIPOR2*) have higher serum triglyceride concentrations [40]. In the study carried out by Kotronen *et al*. (2009), another SNP in *ADIPOR2* (rs767870) was associated with increased levels of triglycerides in men without lipid-lowering medication [63]. Recently, Castilhos *et al*. (2015) found two *ADIPOR2* SNPs (rs11061925 and rs929434), but none of the two in *ADIPOR1* were associated with serum triglycerides in men infected with HIV under anti-retroviral treatment [66].

Most authors have suggested that the molecular mechanism behind these genetic associations with serum triglycerides is related to the metabolic effects of adiponectin that increase fatty acid oxidation through AMPK and APPL1 activation [67]. Activation of these pathways leads to enhanced lipolysis and reduced lipid metabolites, which interfere with intracellular insulin signaling [68], favoring insulin sensitivity, and preventing the development of T2DM. Therefore, it is possible that the results from the current study that involve T2DM and hypertriglyceridemia indicate a single phenomenon instead of two independent genotype/phenotype relationships. To solve this issue, a novel logistic regression model adjusted by T2DM prevalence (as well as sex and age) was performed, and the association between rs10494839 and high serum triglycerides remained statistically significant ($p = 0.013$). Additionally, when subjects with T2DM were excluded, this relationship also remained statistically significant ($p = 0.026$). Therefore, these findings support further studies focused on the potential role of AdipoR1 and adiponectin in the treatment of high serum triglycerides. It is rational to approach the effects of pharmacologic stimuli on liposome and lipid droplet formation in humans.

Another remarkable finding involving rs2275737 indicates that HDLc concentrations were lower in subjects with the AA genotype and also in the group with AA+AC genotypes ($p < 0.01$; **Table A3**). Regarding this relationship, Jin *et al*. (2014) found previously that subjects with T2DM and risk genotypes (GG+GA) in rs3737884 had lower concentrations of HDLc in a genetic association study [53]. Similarly, Yeh *et al*. (2008) reported that a variant in the regulatory region of *ADIPOR1* is associated with lower HDLc in Brazilian subjects with African ancestry [64].

Although adiponectin level medians were associated with the rs2275737 SNP (**Table A3**), no associations between a metabolic trait and plasma levels of adiponectin were found. In contrast, several authors have described associations:

1. Chen *et al*. (2017) showed that Adiponectin is inversely associated with the metabolic syndrome and high arterial stiffness [69].
2. Some population studies have revealed a correlation between plasma levels of adiponectin and HDLc, as was observed by Medina-Urrutia *et al*. (2015), who showed that low adiponectin levels are closely related to low serum HDLc in adults with Mexican-Mestizo ancestry [70].
3. In Japanese individuals, Matsushita *et al*. (2014) found a similar phenomenon [71], and Hanley *et al*. (2007) showed that adiponectin levels are positively associated with HDLc in Hispanics and African-Americans [72].

As expected, anti-dyslipidemic therapy has been observed to influence adiponectin secretion. Statins and fibrates have been generally found to increase adiponectin levels in groups under medical treatment [73]. Thus, it is reasonable to suspect a biological interaction between these genetic variations and the adiponectin release induced by pharmacological activity of statins and fibrates, which may be a research focus in future studies.

Despite the statistically significant results, there are some limitations that should be considered. Firstly, the sample size in the current study was small, which may be a confounding issue in proposing definitive genotype/phenotype relationships. Nonetheless, it was possible to identify consistent genetic associations, even after application of admixture-adjustment methods, suggesting that sampling strategies could have corrected related

bias. Therefore, an expansion of the present sample is strongly encouraged to obtain results from a study with greater predictive power. Secondly, an elevated proportion of the current sample had hypertriglyceridemia; this finding could be a consequence of selection bias. Therefore, further case-control studies would be helpful to verify the actual nature of the genetic relationships described in this study. As a matter of fact, an expanded sample (n = 1,500) of the same population has been analyzed, and similar frequencies of high serum triglycerides and other metabolic alterations have been found (awaiting publication), suggesting that acquired dyslipidemia may be an issue of particular relevance in the population.

In summary, according to the results of the present study and previous data, consistent evidence has been found for an association between genetic variations in *ADIPOR1* with high serum triglycerides and T2DM. These findings encourage future studies on potential biological and pharmacogenomic interactions.

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■ Appendix

Table A1. Single nucleotide polymorphisms selected in the adiponectin receptor 1 gene (*ADIPOR1*) employing data from the 1000 genome project

SNP	Reference variation	Position	Distance (pb)	Allele minor frequency
rs10494839*	C/T	202,922,194	-	0.285
rs75114693	C/T	202,922,125	-69	0.285
rs10920533	A/G	202,925,818	3,624	0.285
rs10920534	C/T	202,927,069	4,875	0.285
rs2275737*	A/C	202,920,300	-	0.449
rs2275738	C/T	202,920,304	4	0.449
rs7514221	C/T	202,926,513	6,213	0.449
rs12733285*	C/T	202,922,040	-	0.306
rs1342386	A/G	202,914,553	-	0.468
rs1342387	A/G	202,914,356	-197	0.468
rs10800887	C/T	202,924,936	-	0.355
rs7517286	C/T	202,927,507	2,571	0.355
rs10800886	C/T	202,922,391	-	0.290
rs1539355	A/G	202,924,080	1,689	0.290
rs61822681	A/G	202,918,536	-3,855	0.290
rs7544565	C/T	202,916,737	-	0.304
rs2364569	C/T	202,916,086	-	0.287
rs12084955	C/T	202,921,631	-	0.286
rs12045862	A/C/T	202,916,806	-	0.262
rs2001831	G/T	202,916,481	-	0.451
rs7539542	C/G	202,909,974	-	0.322
rs33942950	A/G/T	202,917,197	-	0.261

Legend: A total of 22 SNPs were observed in *ADIPOR1*, using the bioinformatic resource SNiPA. Several of the variants were found in linkage disequilibrium (LD) with each other taking into account a correlation coefficient (r^2) = 1.0. The dotted lines denote the groups of SNPs in LD. Two of the genotyped SNPs were in LD with five of the 22 variants: rs10494839 with three (rs75114693, rs10920533, rs10920534) and rs227557 with two (rs227538, rs7514221). For this selection, a minor allele frequency > 0.25 was used. *Genotyped SNPs.

Table A2. Single nucleotide polymorphisms selected in the adiponectin receptor 2 gene (*ADIPOR2*) employing data from the 1000 genome project

SNP	Reference variation	Proxy position	Distance (pb)	Allele minor frequency
rs11061937	C/T	1,816,613	-	0.349
rs11061919	C/T	1,802,625	-13,988	0.349
rs10773986	A/G	1,841,324	24,711	0.349
rs11061923	A/G	1,802,803	-13,810	0.349
rs7975826	C/T	1,802,061	-14,552	0.349
rs2286383	A/G	1,891,372	-	0.478
rs9805049	A/C	1,893,650	2,278	0.478
rs11612383	A/G	1,831,355	-	0.311
rs10082811	C/T	1,863,865	-	0.461
rs1029629	A/C	1,799,267	-	0.33
rs1044471	C/T	1,896,956	-	0.47
rs1058322	C/T	1,836,979	-	0.344
rs10735002	A/C	1,856,227	-	0.44
rs10735003	C/T	1,880,385	-	0.5
rs4766415	A/T	1,878,154	-2,231	0.5
rs10744551	A/T	1,857,421	-	0.464
rs10773980	C/T	1,798,718	-	0.499
rs10773982	A/G	1,828,149	-	0.372
rs10773983	A/G	1,831,246	-	0.304
rs12316367	A/G	1,850,146	-	0.449
rs10848563	C/T	1,841,543	-8,603	0.449
rs10773988	A/G	1,856,181	6,035	0.449
rs10773989	C/T	1,856,982	-	0.47
rs10773991	C/T	1,885,306	-	0.499
rs10848553	C/T	1,802,316	-	0.312
rs11061920	C/T	1,802,661	345	0.312
rs11061921	C/T	1,802,734	418	0.312
rs11061924	C/G	1,803,006	690	0.312
rs11061927	C/G	1,805,467	3,151	0.312
rs11061957	A/T	1,845,237	42,921	0.312
rs11061962	C/G	1,855,824	53,508	0.312
rs1136213	A/G	1,804,285	1,969	0.312
rs11832817	C/T	1,817,142	14,826	0.312
rs12230579	A/T	1,817,073	14,757	0.312
rs12231894	A/G	1,853,562	51,246	0.312
rs12582624	C/G	1,842,143	39,827	0.312
rs12810020	C/T	1,829,903	27,587	0.312
rs2058034	C/T	1,804,700	2,384	0.312
rs2058035	C/T	1,803,521	1,205	0.312
rs6489323	A/G	1,813,758	11,442	0.312
rs6489324	A/C	1,819,559	17,243	0.312
rs66590925	A/G	1,851,286	48,970	0.312
rs7132033	C/G/T	1,806,096	3,780	0.312
rs78966828	C/T	1,837,622	35,306	0.312
rs10848557	G/T	1,827,810	-	0.498
rs7296521	C/T	1,802,988	-24,822	0.498
rs9739162	G/T	1,838,008	10,198	0.498
rs10848558	A/G	1,830,291	-	0.371
rs7978818	A/C	1,821,608	-8,683	0.371
rs11061940	C/T	1,822,392	-7,899	0.371
rs10848560	C/T	1,839,492	-	0.5
rs10848561	A/G	1,839,493	-	0.478
rs10848565	C/G	1,843,410	-	0.449
rs10848569	A/G	1,860,541	-	0.346

Table A2. Continued

SNP	Reference variation	Proxy position	Distance (pb)	Allele minor frequency
rs10848571	G/T	1,882,472	-	0.48
rs11061925	C/T	1,803,234	-	0.334
rs11061968	A/G/T	1,859,103	-	0.347
rs11061971	A/T	1,863,728	-	0.478
rs11061972	C/T	1,863,862	-	0.343
rs11061974	A/G	1,867,017	-	0.346
rs11614639	G/T	1,883,689	-	0.473
rs12342	A/G	1,896,880	-	0.347
rs12831353	A/G	1,875,765	-21,115	0.347
rs12828908	A/G	1,879,385	-17,495	0.347
rs12812707	G/T	1,884,245	-12,635	0.347
rs2286385	C/T	1,890,589	-6,291	0.347
rs3809266	A/C	1,894,141	-2,739	0.347
rs12813694	C/T	1,875,630	-	0.345
rs2068485	G/T	1,868,527	-	0.474
rs2068491	A/C/G	1,847,870	-	0.479
rs7976827	C/T	1,841,939	-	0.479
rs6489326	C/T	1,842,237	-	0.479
rs10848567	A/T	1,845,697	-2,173	0.479
rs2108642	G/T	1,866,799	-	0.498
rs9300298	A/T	1,866,204	-595	0.498
rs2190556	C/T	1,833,912	-	0.479
rs2240613	A/G	1,892,816	-	0.348
rs7294668	C/T	1,878,535	-	0.499
rs2370055	C/T	1,887,698	-	0.312
rs34375871	A/G	1,851,214	-	0.313
rs3759374	A/G	1,886,643	-	0.48
rs7974422	A/G	1,885,262	1,381	0.48
rs4140992	C/T	1,836,812	-	0.462
rs4765842	A/G	1,857,694	-	0.365
rs4765843	C/T	1,868,726	-	0.499
rs4765844	A/G	1,874,853	-	0.492
rs4766413	A/G	1,833,788	-	0.313
rs539426413	A/C	1,864,020	-	0.435
rs557507060	A/T	1,864,026	-	0.435
rs7135363	A/T	1,804,669	-	0.238
rs7294668	C/T	1,878,535	-	0.499
rs2286384	C/G	1,891,043	12,508	0.499
rs568814490	G/T	1,864,016	-	0.445
rs7297509	C/G	1,848,977	-	0.311
rs730032	C/T	1,895,372	-	0.25
rs7306506	C/T	1,886,544	-	0.442
rs7313760	C/G	1,870,712	-	0.345
rs7964003	C/G	1,821,393	-	0.298
rs7974924	A/T	1,872,277	-	0.477
rs7978362	C/G	1,865,574	6,703	0.477
rs7978783	A/G	1,858,719	-	0.498
rs929434	C/T	1,862,089	-	0.347

Legend: A total of 101 SNPs were observed in *ADIPOR2*, using the bioinformatic resource SNiPA. Several of the variants were found in linkage disequilibrium (LD) with each other taking into account a correlation coefficient (r^2) = 1.0. The dotted lines denote the groups of SNPs in LD. Five of the genotyped SNPs were in LD with five of the 101 variants: rs11061937 with four (rs11061919, rs10773986, rs11061923, rs7975826) and rs2286383 with one (rs9805049). For this selection, a minor allele frequency > 0.25 was used. *Genotyped SNPs.

Table A3. Mean values of anthropometric and biochemistry parameters according to the genotype for *ADIPOR1* SNPs

Variable	rs10494859													
	CC		CT		TT		p	TT+CT		p†	CC+CT		p†	
Body mass index (kg/m²)	28.7	[27.70 - 29.57]	24.7	[21.15 - 27.75]	24.8	[21.9 - 27.7]	0.016*	24.7	[21.85 - 27.43]	0.09*	25.1	[21.9 - 27.6]		0.466
Waist circumference (cm)	94.6	±9.1	87.3	±14.3	87.9	±13.6	0.285	87.7	±13.6	0.09*	88.3	±13.4		0.852
Blood pressure														
Systolic (mmHg)	115.0	[110 - 119.5]	110.0	[100.0 - 113.5]	110.0	[100.0 - 120.0]	0.125	110.0	[100.0 - 118.0]	0.152	110.0	[100.0 - 118.0]		0.331
Diastolic (mmHg)	78.0	[70.0 - 83.0]	70.0	[64.0 - 79.5]	74.0	[68.0 - 80.0]	0.093	70.0	[66.0 - 80.0]	0.139	70.0	[68.0 - 80.0]		0.271
Serum concentration														
Glucose (mg/dl)	89.5	[82.0 - 92.75] (5.0 [4.6 - 5.2])	87.0	[84.0 - 95.75] (4.8 [4.7 - 5.3])	91.0	[86.0 - 96.0] (5.1 [4.8 - 5.3])	0.085	90.0	[86.0 - 96.0] (5.0 [4.8 - 5.3])	0.504	87.5	[84.0 - 95.25] (4.9 [4.7 - 5.3])		0.02*
Triglycerides (mg/dl)	174.0	[158.5 - 182.8] (2.0 [1.8 - 2.1])	168.0	[149.0 - 192.0] (1.9 [1.7 - 2.2])	175.0	[161.0 - 193.0] (2.0 [1.8 - 2.2])	0.150	173.0	[156.5 - 192.5] (2.0 [1.8 - 2.2])	0.669	179.0	[149.0 - 191.2] (2.0 [1.7 - 2.2])		0.05
HDLc (mg/dl)	50.5	[48.25 - 51.75] (1.3 [1.2 - 1.3])	48.0	[46.0 - 51.0] (1.2 [1.2 - 1.3])	47.0	[45.0 - 50.0] (1.2 [1.2 - 1.3])	0.086	47.0	[45.0 - 51.0] (1.2 [1.2 - 1.3])	0.047*	48.0	[46.0 - 51.25] (1.2 [1.2 - 1.3])		0.13
Insulin (uU/ml)	10.0	[10.0 - 11.28] (71.8 [71.8 - 84.5])	10.0	[10.0 - 10.97] (71.8 [71.8 - 78.1])	10.0	[10.0 - 12.40] (71.8 [71.8 - 89.0])	0.062	10.0	[10.0 - 11.53] (71.8 [71.8 - 82.9])	0.04	10.0	[10.0 - 11.25] (71.8 [71.8 - 80.71])		0.062
Adiponectin (µg/ml)	14.5	[12.2 - 18.6]	15.8	[13.6 - 19.32]	15.3	[12.32 - 18.77]	0.300	15.5	[12.5 - 19.02]	0.622	15.7	[13.4 - 19.18]		0.260
HbA1c (%)	5.0	[4.5 - 6.025]	5.0	[4.7 - 6.0]	5.0	[4.0 - 6.0]	0.942	5.0	[4.2 - 6.0]	0.783	5.0	[4.7 - 6.0]		0.904
HOMAiR	2.35	[2.65 - 2.75]	2.2	[2.0 - 2.65]	2.3	[2.1 - 3.0]	0.419	2.3	[2.1 - 3.0]	0.884	2.2	[2.0 - 2.725]		0.226
	rs12733285													
	TT		TC		CC		p	CC+CT		p†	TT+CT		p†	
Body mass index (kg/m²)	25.2	[22.4 - 31.8]	24.45	[22.52 - 27.4]	25.00	[21.6 - 27.6]	0.864	24.9	[21.9 - 27.6]		24.50	[22.5 - 27.7]		0.877
Waist circumference (cm)	92.7	±12.9	87.5	±13.9	88.0	±12.8	0.485	87.8	±13.2	0.384	88.2	±14.4		0.912
Blood pressure														
Systolic (mmHg)	110.0	[101.0 - 124.0]	110.0	[100.0 - 118.0]	110.0	[100.0 - 118.0]	0.839	110.0	[100.0 - 118.0]	0.633	110.0	[100.0 - 118.0]		0.632
Diastolic (mmHg)	70.0	[66.0 - 86.0]	70.0	[64.0 - 80.0]	70.0	[68.0 - 80.0]	0.861	70.0	[68.0 - 80.0]	0.665	70.0	[64.0 - 80.0]		0.853
Serum concentration														
Glucose (mg/dl)	89.0	[87.0 - 90.5] (4.9 [4.8 - 5.0])	91.0	[86.0 - 96.0] (5.1 [4.8 - 5.3])	90.0	[84.0 - 96.0] (5.0 [4.7 - 5.3])	0.47	90.0	[85.0 - 96.0] (5.0 [4.7 - 5.3])	0.686	90.5	[86.0 - 96.0] (5.0 [4.8 - 5.3])		0.324
Triglycerides (mg/dl)	192.0	[185.5 - 196.5] (2.2 [2.1 - 2.2])	173.0	[154.5 - 192.0] (2.0 [1.7 - 2.2])	173.0	[156.0 - 189.0] (2.0 [1.8 - 2.1])	0.025*	173.0	[155.2 - 191.0] (2.0 [1.8 - 2.2])	0.05*	175.5	[158.2 - 193.8] (2.0 [1.8 - 2.2])		0.319
HDLc (mg/dl)	47.0	[46.5 - 50.5] (1.2 [1.2 - 1.3])	47.0	[45.5 - 50.0] (1.2 [1.2 - 1.3])	48.0	[45.0 - 51.5] (1.2 [1.2 - 1.3])	0.802	48.0	[45.0 - 51.0] (1.2 [1.2 - 1.3])	0.973	47.0	[46.0 - 50.0] (1.2 [1.2 - 1.3])		0.520
Insulin (uU/ml)	10.0	[10.0 - 11.6] (71.8 [71.8 - 83.2])	10.0	[10.0 - 10.8] (71.8 [71.8 - 77.5])	10.0	[10.0 - 11.85] (71.8 [71.8 - 85.0])	0.874	10.0	[10.0 - 11.6] (71.8 [71.8 - 83.2])	0.960	10.0	[10.0 - 10.8] (71.8 [71.8 - 77.5])		0.612
Adiponectin (µg/ml)	15.5	[13.15 - 17.5]	15.1	[12.4 - 17.75]	15.7	[12.88 - 19.4]	0.435	15.5	[12.5 - 19.15]	0.712	15.15	[12.5 - 17.88]		0.197
HbA1c (%)	5.0	[4.0 - 5.0]	5.0	[4.0 - 6.0]	5.0	[4.075 - 6.0]	0.143	5.0	[4.275 - 6.0]	0.967	5.0	[4.0 - 6.0]		0.217
HOMAiR	2.2	[2.1 - 2.35]	2.3	[2.1 - 2.9]	2.3	[2.0 - 3.0]	0.528	2.3	[2.1 - 3.0]	0.748	2.3	[2.1 - 2.8]		0.335
	rs2275737													
	AA		AC		CC		p	CC+AC		p†	AA+AC		p†	
Body mass index (kg/m²)	24.8	[21.9 - 27.00]	24.8	[22.68 - 27.4]	25.1	[21.4 - 28.5]	0.949	24.9	[21.9 - 27.8]	0.804	24.8	[22.5 - 27.2]		0.775
Waist circumference (cm)	87.0	±12.0	88.3	±12.4	88.3	±15.4	0.867	88.3	±13.8	0.559	87.9	±12.2		0.844
Blood pressure														
Systolic (mmHg)	110.0	[100.0 - 110.0]	110.0	[100.0 - 114.0]	110.0	[100.0 - 120.0]	0.157	110.0	[100.0 - 120.0]	0.314	110.0	[100.0 - 112.0]		0.057
Diastolic (mmHg)	70.0	[62.0 - 80.0]	70.0	[64.0 - 80.0]	70.0	[70.0 - 80.0]	0.633	70.0	[68.0 - 80.0]	0.444	70.0	[64.0 - 80.0]		0.411
Serum concentration														
Glucose (mg/dl)	89.5	[86.0 - 96.0] (5.0 [4.8 - 5.3])	91.0	[86.0 - 96.00] (5.1 [4.8 - 5.3])	89.0	[84.0 - 93.5] (4.9 [4.7 - 5.2])	0.344	90.0	[85.0 - 96.0] (5.0 [4.7 - 5.3])	0.839	91.0	[86.0 - 96.0] (5.1 [4.8 - 5.3])		0.155
Triglycerides (mg/dl)	183.5	[172.8 - 193.0] (2.1 [2.0 - 2.2])	173.0	[156.0 - 193.0] (2.0 [1.8 - 2.2])	170.0	[154.0 - 184.5] (1.9 [1.7 - 2.1])	0.061	172.0	[154.0 - 191.0] (1.9 [1.7 - 2.2])	0.05*	173.0	[160.0 - 193.0] (2.0 [1.8 - 2.2])		0.109
HDLc (mg/dl)	47.0	[45.00 - 49.25] (1.2 [1.2 - 1.3])	47.0	[46.0 - 50.0] (1.2 [1.2 - 1.3])	50.0	[46.0 - 52.5] (1.3 [1.2 - 1.3])	0.020*	48.0	[46.0 - 51.0] (1.2 [1.2 - 1.3])	0.132	47.0	[45.0 - 50.0] (1.2 [1.2 - 1.3])		0.006*
Insulin (uU/ml)	10.0	[10.0 - 13.30] (71.8 [71.8 - 95.4])	10.0	[10.0 - 10.30] (71.8 [71.8 - 73.9])	10.0	[10.0 - 11.5] (71.8 [71.8 - 82.5])	0.275	10.0	[10.0 - 11.3] (71.8 [71.8 - 81.1])	0.120	10.0	[10.0 - 11.55] (71.8 [71.8 - 85.6])		0.830
Adiponectin (µg/ml)	15.4	[11.8 - 15.6]	15.5	[12.5 - 18.7]	16.4	[13.55 - 19.62]	0.004*	15.8	[13.0 - 19.4]	0.02*	14.85	[12.30 - 18.07]		0.022*
HbA1c (%)	5.0	[4.0 - 6.0]	5.0	[4.825 - 6.0]	5.0	[4.05 - 6.4]	0.396	5.0	[4.5 - 6.0]	0.167	5.0	[4.35 - 6.0]		0.321
HOMAiR	2.4	[2.1 - 3.35]	2.2	[2.1 - 2.8]	2.2	[2.0 - 2.85]	0.141	2.2	[2.1 - 2.8]	0.075	2.3	[2.1 - 3.0]		0.141

Legend: Data are median (1st quartile - 3rd quartile), mean ± SD.

Table A4. Mean values of anthropometric and biochemistry parameters according to the genotype for *ADIPOR2* SNPs

rs11061937

Variable	CC		CT		TT		p	TT+CT		p †	CC+CT		p †
Body mass index (kg/m^2)	25.0	[20.9 - 27.80]	24.95	[21.75 - 28.15]	24.7	[22.1 - 27.3]	0.967	24.9	[21.9 - 27.6]	0.937	25.0	[21.65 - 28.05]	0.834
Waist circumference (cm)	87.5	±14.5	87.3	±14.3	87.9	±13.6	0.285	87.7	±13.6	0.829	88.0	±13.9	0.927
Blood pressure													
Systolic (mmHg)	110.0	[100.0 - 117.5]	110.0	[100.0 - 118.0]	110.0	[100.0 - 117.0]	0.767	110.0	[100.0 - 118.0]	0.678	110.0	[100.0 - 119.0]	0.661
Diastolic (mmHg)	70.0	[60.0 - 80.0]	72.0	[68.0 - 80.0]	70.0	[68.5 - 80.0]	0.504	70.0	[68.0 - 80.0]	0.265	70.0	[66.0 - 80.0]	0.990
Serum concentration													
Glucose (mg/dl)	90.0	[87.0 - 93.0] (5.0 [4.8 - 5.2])	91.0	[86.0 - 96.0] (5.1 [4.8 - 5.3])	89.5	[85.0 - 96.75] (5.0 [4.7 - 5.4])	0.967	90.0	[85.0 - 96.0] (5.0 [4.7 - 5.3])	0.915	91.0	[86.0 - 96.0] (5.1 [4.8 - 5.3])	0.797
Triglycerides (mg/dl)	173.0	[160.0 - 182.0] (2.0 [1.8 - 2.1])	175.0	[154.2 - 194.8] (2.0 [1.7 - 2.2])	173.0	[156.5 - 192.0] (2.0 [1.8 - 2.2])	0.79	173.5	[155.8 - 193.0] (2.0 [1.8 - 2.2])	0.534	174.0	[156.5 - 192.0] (2.0 [1.8 - 2.2])	0.930
HDLc (mg/dl)	48.0	[46.0 - 50.0] (1.2 [1.2 - 1.3])	48.0	[45.25 - 51.0] (1.2 [1.2 - 1.3])	47.0	[45.0 - 51.0] (1.2 [1.2 - 1.3])	0.910	48.0	[45.0 - 51.0] (1.2 [1.2 - 1.3])	0.818	48.0	[45.5 - 51.0] (1.2 [1.2 - 1.3])	0.675
Insulin (μU/ml)	10.0	[10.0 - 11.8] (71.8 [71.8 - 84.7])	10.0	[10.0 - 11.88] (71.8 [71.8 - 85.2])	10.0	[10.0 - 10.85] (71.8 [71.8 - 77.8])	0.44	10.0	[10.0 - 11.55] (71.8 [71.8 - 82.9])	0.21	10.0	[10.0 - 11.9] (71.8 [71.8 - 85.4])	0.53
Adiponectin (μg/ml)	16.5	[13.3 - 19.2]	15.65	[13.12 - 19.07]	14.3	[12.05 - 18.20]	0.224	15.4	[12.5 - 18.8]	0.635	15.7	[13.15 - 19.15]	0.084
HbA1c (%)	5.0	[4.6 - 5.8]	5.0	[4.2 - 6.025]	5.0	[4.0 - 6.0]	0.481	5.0	[4.175 - 6.0]	0.25	5.0	[4.2 - 6.0]	0.996
HOMA-IR	2.2	[2.1 - 2.6]	2.3	[2.1 - 2.8]	2.2	[2.1 - 3.075]	0.844	2.3	[2.1 - 3.0]	0.573	2.3	[2.1 - 2.8]	0.974

rs11612383

Variable	AA		AG		GG		p	GG+AG		p †	AAAG		p †
Body mass index (kg/m^2)	25.1	[19.77 - 27.38]	24.6	[21.65 - 27.85]	25.1	[22.5 - 27.7]	0.621	24.9	[21.98 - 27.77]	0.521	24.7	[21.5 - 27.6]	0.38
Waist circumference (cm)	83.2	±13.4	87.0	±14.1	90.4	±12.5	0.067	88.5	±13.4	0.119	86.4	±14.0	0.038*
Blood pressure													
Systolic (mmHg)	109.0	[98.5 - 116.0]	110.0	[100.0 - 118.0]	110.0	[100.0 - 118.0]	0.516	110.0	[100.0 - 118.0]	0.371	110.0	[100.0 - 118.0]	0.350
Diastolic (mmHg)	70.0	[65.5 - 80.0]	70.0	[68.0 - 80.0]	74.0	[68.0 - 80.0]	0.423	70.0	[68.0 - 80.0]	0.572	70.0	[67.0 - 80.0]	0.197
Serum concentration													
Glucose (mg/dl)	87.5	[85.0 - 96.0] (4.9 [4.7 - 5.3])	91.5	[86.0 - 96.0] (5.1 [4.8 - 5.3])	89.0	[85.0 - 95.0] (4.9 [4.7 - 5.3])	0.266	90.0	[86.0 - 96.0] (5.0 [4.8 - 5.3])	0.447	91.0	[86.0 - 96.0] (5.1 [4.8 - 5.3])	0.235
Triglycerides (mg/dl)	171.0	[155.2 - 203.5] (1.9 [1.8 - 2.3])	172.0	[154.5 - 187.8] (1.9 [1.7 - 2.1])	176.0	[159.0 - 193.0] (2.0 [1.8 - 2.2])	0.25	173.0	[156.5 - 191.5] (2.0 [1.8 - 2.2])	0.614	172.0	[154.0 - 190.2] (1.9 [1.7 - 2.1])	0.127
HDLc (mg/dl)	49.5	[45.25 - 51.75] (1.3 [1.2 - 1.3])	48.0	[46.0 - 51.0] (1.2 [1.2 - 1.3])	47.0	[45.0 - 50.0] (1.2 [1.2 - 1.3])	0.539	48.0	[45.0 - 51.0] (1.2 [1.2 - 1.3])	0.679	48.0	[46.0 - 51.0] (1.2 [1.2 - 1.3])	0.269
Insulin (μU/ml)	10.0	[10.0 - 10.22] (71.8 [71.8 - 73.3])	10.0	[10.0 - 12.4] (71.8 [71.8 - 89.0])	10.0	[10.0 - 10.5] (71.8 [71.8 - 75.3])	0.727	10.0	[10.0 - 12.0] (71.8 [71.8 - 86.1])	0.798	10.0	[10.0 - 12.2] (71.8 [71.8 - 87.5])	0.507
Adiponectin (μg/ml)	16.25	[13.72 - 18.85]	15.5	12.5 - 19.25]	15.3	[12.4 - 18.4]	0.686	15.45	[12.5 - 18.85]	0.418	15.6	[12.5 - 19.2]	0.607
HbA1c (%)	5.0	[4.0 - 5.0]	5.05	[4.0 - 6.0]	5.0	[4.8 - 6.0]	0.241	5.0	[4.275 - 6.0]	0.092	5.0	[4.0 - 6.0]	0.561
HOMA-IR	2.2	[2.1 - 2.4]	2.3	[2.1 - 3.075]	2.2	[2.1 - 2.9]	0.449	2.3	[2.1 - 3.0]	0.554	2.3	[2.1 - 3.0]	0.356

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Variable	AA		AG		GG		p	CGGAG		p †	AAAAG		p †
Body mass index (kg/m^2)	25.3	[23.05 - 28.75]	24.75	[22.43 - 27.4]	24.9	[20.6 - 28.25]	0.417	24.8	[21.6 - 27.6]	0.222	24.9	[22.6 - 27.5]	0.424
Waist circumference (cm)	94.8	±16.2	88.2	±13.1	86.2	±12.9	0.044*	87.3	±13.0	0.065	89.2	±13.8	0.120
Blood pressure													
Systolic (mmHg)	110.0	[101.0 - 120.0]	110.0	[100.0 - 112.5]	110.0	[100.0 - 120.0]	0.497	110.0	[100.0 - 118.0]	0.361	110.0	[100.0 - 114.]	0.616
Diastolic (mmHg)	70.0	[70.0 - 80.0]	70.0	[68.0 - 80.0]	70.0	[64.0 - 80.0]	0.916	70.0	[68.0 - 80.0]	0.874	70.0	[68.0 - 80.0]	0.678
Serum concentration													
Glucose (mg/dl)	92.0	[87.0 - 96.0] (5.1 [4.8 - 5.3])	90.0	[85.0 - 96.0] (5.0 [4.7 - 5.3])	89.0	[85.0 - 94.5] (4.9 [4.7 - 5.3])	0.521	90.0	[85.0 - 96.0] (5.0 [4.7 - 5.3])	0.335	90.0	[86.0 - 96.0] (5.0 [4.8 - 5.3])	0.401
Triglycerides (mg/dl)	181.0	[156.5 - 193.0] (2.0 [1.8 - 2.2])	173.0	[159.0 - 192.0] (2.0 [1.8 - 2.2])	173.0	[152.0 - 187.5] (2.0 [1.7 - 2.1])	0.654	173.0	[156.2 - 191.8] (2.0 [1.8 - 2.2])	0.806	173.0	[159.0 - 192.0] (2.0 [1.8 - 2.2])	0.357
HDLc (mg/dl)	49.0	[45.0 - 51.5] (1.3 [1.2 - 1.3])	48.0	[45.0 - 51.0] (1.2 [1.2 - 1.3])	47.0	[45.5 - 50.5] (1.2 [1.2 - 1.3])	0.637	48.0	[45.25 - 51.0] (1.2 [1.2 - 1.3])	0.488	48.0	[45.0 - 51.0] (1.2 [1.2 - 1.3])	0.420
Insulin (μU/ml)	10.0	[9.6 - 10.0] (71.8 [68.9 - 71.8])	10.0	[10.0 - 12.6] (71.8 [71.8 - 90.4])	10.0	[10.0 - 11.45] (71.8 [71.8 - 82.2])	0.033*	10.0	[10.0 - 12.0] (71.8 [71.8 - 86.1])	0.022*	10.0	[10.0 - 12.0] (71.8 [71.8 - 86.1])	0.513
Adiponectin (μg/ml)	14.3	[11.75 - 19.9]	15.25	12.47 - 18.88]	15.7	[12.95 - 18.75]	0.848	15.6	[12.55 - 18.8]	0.684	15.1	[12.45 - 19.2]	0.620
HbA1c (%)	5.6	[4.0 - 6.6]	5.0	[4.8 - 6.0]	5.0	[4.0 - 6.0]	0.200	5.0	[4.2 - 6.0]	0.254	5.1	[4.65 - 6.0]	0.104
HOMA-IR	2.2	[1.95 - 2.6]	2.3	[2.1 - 3.1]	2.2	[2.0 - 2.55]	0.242	2.3	[2.1 - 3.0]	0.254	2.3	[2.1 - 3.1]	0.366

Legend: Data are median (1st quartile - 3rd quartile), mean ± SD.

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