# UNIVERSIDAD AUTÓNOMA DE GUERRERO

**UNIDAD ACADÉMICA DE CIENCIAS QUÍMICO BIOLÓGICAS**
**UNIDAD ACADÉMICA DE MEDICINA**
**UNIDAD DE INVESTIGACIÓN ESPECIALIZADA EN MICROBIOLOGÍA**
**MAESTRÍA EN CIENCIAS BIOMÉDICAS**


## “POLIMORFISMOS EN LOS GENES DE ADIPONECTINA (RS1501299) Y DE SU RECEPTOR 2 (RS767870) ASOCIADOS AL SÍNDROME METABÓLICO”

T E S I S

QUE PARA OBTENER EL GRADO DE
MAESTRÍA EN CIENCIAS BIOMÉDICAS

P R E S E N T A :


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**UNIVERSIDAD AUTÓNOMA DE GUERRERO**
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APROBACIÓN DE TESIS

En la ciudad de Chilpancingo, Guerrero, siendo los 22 días del mes de junio de dos mil doce, se reunieron los miembros del Comité Tutoral designado por la Academia de Posgrado de la Maestría en Ciencias Biomédicas, para examinar la tesis titulada **"Polimorfismos en los genes de adiponectina (rs1501299) y de su receptor 2 (rs767870) asociados al síndrome metabólico"**, presentada por la alumna Diana Lizzete Antúnez Ortíz, para obtener el Grado de Maestría en Ciencias Biomédicas. Después del análisis correspondiente, los miembros del comité manifiestan su aprobación de la tesis, autorizan la impresión final de la misma y aceptan que, cuando se satisfagan los requisitos señalados en el Reglamento General de Estudios de Posgrado e Investigación Vigente, se proceda a la presentación del examen de grado.

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ESTE TRABAJO SE REALIZÓ EN EL LABORATORIO DE ENFERMEDADES CRÓNICO DEGENERATIVAS DE LA UNIDAD ACADÉMICA DE CIENCIAS QUÍMICO BIOLÓGICAS DE LA UNIVERSIDAD AUTÓNOMA DE GUERRERO EN CHILPANCINGO, GUERRERO, MÉXICO.

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# Haplotypes in *ADIPOQ* and *ADIPOR2* genes associated with metabolic syndrome and atherogenic risk factors in women in the southeast of Mexico

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# Haplotypes in *ADIPOQ* and *ADIPOR2* genes associated with metabolic syndrome and atherogenic risk factors in women in the southeast of Mexico

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## Abstract

**Background:** Adiponectin stimulates fatty acid oxidation, reduces triglycerides, improves glucose metabolism and exerts a protective effect on blood vessels due to its effect anti-inflammatory and anti-atherogenic. Variation in the *ADIPOQ* and *ADIPOR2* genes have been associated with increased risk of developing metabolic syndrome (MS), type-2 diabetes (T2D), or coronary heart disease. The aim of this study was to evaluate the association of variants in *ADIPOQ* and *ADIPOR2* genes and adiponectin levels with MS or phenotypes atherogenic risk in women in the southeast of Mexico.

**Methods:** Anthropometric measurements, blood pressure, fasting glucose, triglycerides, total cholesterol, LDL-c, and HDL-c were performed. Genotyping was based on the 5'-nuclease assay, using the combined PCR with TaqMan fluorogenic assay specific for each single nucleotide polymorphism (SNP).

**Results:** Adiponectin levels were higher in women without MS (13.5 vs. 4.6 µg/ml) and were negatively correlated with age, waist circumference, blood pressure, glucose, triglycerides and CHD risk score, and positively with HDL cholesterol

(HDL-chol). Women who were carriers of the haplotype ATC in *ADIPOQ* gene were 4.4 times more likely to have elevated levels of atherogenic LDL-chol, while the AGT haplotype was associated with increased levels of HDL-chol and CTT haplotype with increased levels of adiponectin. Regarding the *ADIPOR2* gene, we observed that the ATA haplotype was associated with an increased risk of MS, while the GTT haplotype with a significant reduction in the average score coronary heart disease (CHD) risk.

**Conclusion:** The findings suggest that variants in genes *ADIPOQ* and *ADIPOR2* are related to the development of metabolic disorders and coronary heart disease.

**Key words:** metabolic syndrome, adiponectin, haplotypes, SNP, coronary heart disease

## Background

Adiponectin is a hormone with anti-diabetics, anti-inflammatory and anti-atherogenic properties, also contribute in regulating the body's energy metabolism by stimulating fatty acid oxidation, reduction of blood triglycerides and improve metabolism of glucose by increasing insulin sensitivity [1, 2]. In obese individuals, type-2 diabetes (T2D), insulin resistance (IR), metabolic syndrome (MS) and cardiovascular disease has been found that serum levels of adiponectin are decreased [3]. Other authors report that there are differences according to gender, being higher in women than in men, and its variation is influenced by age, race and lifestyle [4, 5]. Two adiponectin receptors have been identified, the receptor 1

(ADIPOR1) with a high level of expression in skeletal muscle, and the receptor 2 (ADIPOR2) expressed primarily in the liver [6, 7].

Variants in *ADIPOQ* and *ADIPOR2* genes have been associated with susceptibility to T2D, MS, coronary heart disease (CHD) and different types of cancers, including colorectal, pancreatic, liver, breast, etc. [8, 9]. Several authors have reported the relationship between single nucleotide polymorphism (SNP) rs1501299 *ADIPOQ* gene, with the decrease in the adiponectin levels, increased IR [8, 10] and an increase in the risk of T2D [11, 12]. Subjects homozygous for the G allele have twice risk of developing the disease compared with TT genotype [13]. Besides the SNP rs3821799 is associated with body weight [14] and rs822395 with CHD [15]. Furthermore, the polymorphism rs767870 *ADIPOR2* gene has been associated with an increased incidence of atherosclerosis [16], and higher risk T2D [17]. The rs929434 has been associated with high triglyceride levels [18] and the rs11061971 with T2D [19]. Recent studies have demonstrated the association of polymorphisms in genes *CAPN10, IRS1, TCF7L2, PPARG, ADRB3*, and *SIRT1* in the presence of T2D in Mexican Americans individuals [20-22], but this association with *ADIPOQ* and *ADIPOR2* genes not described in Mexican population.

The MS due to the presence of several cardiovascular risk factors, including insulin resistance, glucose intolerance, central obesity, T2D, dyslipidemia and hypertension, contributes to increased cardiovascular morbidity and premature death. It has been reported that MS is caused by multiple factors related to lifestyle such as overweight and obesity, physical inactivity, excessive consumption of carbohydrates, genetic predisposition, among others [23]. The national health

survey in 2006 (ENSANUT 2006) reported that in Mexico there are 17 million adults with MS, and according to the criteria of the NECP/ATPIII national prevalence is 36.8% higher in women (42.2%) than men (30.3 %) [24]. Therefore, the purpose of this study was to investigate the association between the polymorphism rs1501299, rs3821799 and rs822395 in *ADIPOQ* gene and rs767870, rs929434 and rs11061971 in *ADIPOR2* with the phenotypes of MS and serum adiponectin levels in women in the southeast of Mexico, native and resident of the state of Guerrero.

## Subjects and Methods

*Subjects*

Were studied 346 women from 30 to 65 years old, genetically unrelated, native and resident of the state of Guerrero, Mexico, whose parents and grandparents were also born in the State. They were recruited in their workplaces in the localities of the central area and Acapulco, and was classified as a women with MS who had three or more of the criteria of NCEP-ATPIII [25]: waist circumference ≥ 88 cm, blood pressure ≥ 130/85 mmHg, fasting serum glucose ≥ 110 mg/dl, triglycerides ≥ 150 mg/dl and HDL-c <50 mg/dl. In addition, the score of risk for CHD was determined using the Framingham criteria [26]. Sociodemographic data were obtained through a questionnaire, somatometric measurements were performed and a sample of venous blood was taken after 12 hours fasting. The project was approved by the Committee of Bioethics of the Autonomous University of Guerrero and all women agreed to participate in the study signed the informed consent form.

*Biochemical measurements*

With aliquots of fresh serum were determined the concentrations of glucose, total cholesterol, triglycerides, HDL-c and LDL-c using conventional enzymatic methods with standardized commercial kits (Spinreact). Aliquots of serum were frozen at -20ºC. Adiponectin levels were measured by ELISA technique (Millipore, USA).

*Genotyping*

DNA was extracted from peripheral blood using non-enzymatic rapid technique, and the concentration and purity were evaluated by spectrophotometry. SNPs genotyping was based on the 5´-nuclease assay, using the PCR technique combined with the fluorogenic specific TaqMan for each SNP assay. The reaction was performed on automated equipment 7900HT Fast Real-Time (Applied Biosystems). All assays were made by duplicate and analyzed and determined by graphical display, using the sequence detection system (SDS 2.4 Applied Biosystems).

*Statistical analysis*

Comparison of the sociodemographic characteristics, clinical, and genotype and allele frequencies of SNPs in *ADIPOQ* and *ADIPOR2* genes, using the Chi-square or Mann Whitney test for categorical and continuous variables respectively. We evaluated the Hardy Weinberg equilibrium of different polymorphisms using the chi-square test with one degree of freedom, and calculated Lewontin's D' statistic for linkage disequilibrium between the SNPs. Models of linear and logistic regression were evaluated to determine the association of MS with plasma adiponectin concentration, and genotypes or haplotypes of the polymorphisms studied. All statistical tests were bilateral and a p value of $< 0.05$ was considered

significant. The statistical analysis was carried out in the STATA software (v.11.1). Analysis of haplotypes was performed in the SNPStats software (http://bioinfo.iconcologia.net/SNPstats).

## Results

The prevalence of MS was 31.5%, on average they showed greater blood pressure, BMI, waist circumference, % fat and decrease in the % of water, also elevated fasting glucose, total cholesterol, triglycerides, LDL-c and decreased HDL-c and adiponectin concentration (Table I).

Age, body mass index (BMI), waist circumference, systolic and diastolic blood pressure, glucose and triglycerides concentration, and the CHD risk score were negatively correlated with serum levels of adiponectin, and positively with levels of HDL-c (Table II). It was found that serum adiponectin levels are influenced by the presence of MS, waist circumference, blood pressure and dyslipidemia, but not with glucose level (Table III).

The genotypic distribution of polymorphisms in *ADIPOQ* and *ADIPOR2* genes found in Hardy-Weinberg equilibrium in both study groups, we found no significant differences in the distribution of genotypes and alleles of these polymorphisms among women with or without MS (Table IV). Table V shows the effect of the SNPs on atherogenic risk factors. It is observed that the TT genotype of rs1501299 polymorphism had an effect in reducing CHD risk score ($\beta = -2.6$), while the CC of rs822395 in increasing this score ($\beta = 2.9$). Also observed increased levels of HDL-

c (β = 3.5) and decrease LDL-c (β = -14.8) for TT rs3821799 genotype. It is noted that rs929434 TT genotype influenced increased triglycerides (β = 39.1) and in the reduction of adiponectin (β = -2.1). Significant increases were observed in systolic blood pressure, triglyceride levels and CHD risk score and adiponectin decreased for the AA genotype of rs11061971 (Table V).

Furthermore, it was found that homozygotic women carrying the TT genotype of rs929434 had 2.3 times more risk of having MS compared to women carrying the CC or CT genotypes (OR=2.3; 95%CI: 1.2-4.4), while the carriers of AA genotype of rs11061971 this risk was 2.2 times higher (OR=2.2, 95%CI: 1.0-4.9) compared with carriers TT or TA genotypes (data not shown).

Haplotype analysis of *ADIPOQ* gene polymorphisms showed that the ATC haplotype was associated with LDL-c atherogenic risk (OR=4.4, 95%CI: 1.1-17.7), while the AGT haplotype was associated with a decrease in the concentrations of HDL-c (β=2.9, 95%CI: 0.1-5.6). It is observed that the CTT haplotype had a significant effect on the average increase in serum adiponectin (β=3.5, 95%CI: 0.5-6.4) (Table VI). Regarding the analysis of the haplotypes in the gene *ADIPOR2*, it was observed that the ATA haplotype showed marginal association with increased risk of having MS (OR=1.5, 95%CI: 1.0-2.2, p=0.05), and haplotype GTT significant effect in reducing CHD risk score (β=-2.3, 95%CI: -4.0, -0.5, p=0.011) (data not shown).

## Discussion

The prevalence of MS in our study (31.5%) was lower than that reported by the ENSANUT-2006 (42.2%) [24], however, the average HDL-c levels, an important component of MS, was very low, and the BMI was elevated (27.8 kg/m$^2$). Women with MS had higher average age compared with those who did not have MS, factors such as exercise and smoking appear not to have effect on the MS. The low concentration of adiponectin (4.6 μg/ml) was significantly associated with the presence of MS, suggesting a role of this hormone in the pathophysiology of this syndrome. In a study conducted in Japanese population reported an average adiponectin of 8.2 μg/ml in women and those with levels lower than 4 μg/ml had a higher prevalence of MS components [27]. In Hindu population was found that women with MS showed values less than 6.5 μg/ml and these were correlated with the components of MS [28]. In another study in Mexican-Americans subjects average adiponectin levels were 8.7 μg/ml [29].

The negative relationship between levels of adiponectin and MS, as well as its components (waist circumference, blood pressure and triglyceride levels), suggest a decrease in levels of adiponectin by increasing the presence of these factors, i.e. between more risk factors have a person, in addition to their genetic variants, will have lower levels of this hormone. Obesity is considered to the detonating factor for reducing adiponectin levels, as a result of the inflammatory state, which predominates in obese persons, mainly associated with the levels of TNF-α as an important regulator of adipocyte, due to its effect in decreasing of lipogenesis and increased lipolysis, increasing the levels of circulating fatty acids and exert an

inhibitory effect on adiponectin [30]. It has been shown that adiponectin reduces blood concentrations of free fatty acids and triglycerides, related to the increase in lipid catabolism derived from stimulation of the expression of enzymes involved in the transport and metabolism of fatty acids in the liver and skeletal muscle such as acyl-CoA carboxylase and AMPK [31]. We propose to verify the cause-effect relationship between MS and hypoadiponectinemia in a cohort study.

In the analysis of the polymorphisms found more frequently at GG genotype (57.5%) of SNP rs1501299, CT (75.1%) of rs3821799, AA (56.7%) of rs822395, CT (47%) of rs929434, TT (46.8%) of rs11061971, and AA of rs767870 (82.3%), and most frequently G allele (75.6%), C (52%), A (75.7%), C (60.6%), T (68.5%), and A (90.6%), respectively. Previous studies have associated the rs1501299 polymorphism with the presence of MS or its components [10, 12], IR [8], diabetes [32], high levels of triglycerides and LDL-c [33], or increased CHD [11], the rs3821799 with body weight [14], and rs822395 with CHD [15]. Furthermore rs767870 polymorphism has been associated with T2D [17], atherosclerosis [16] or high triglyceride levels [18], rs929434 with high triglyceride levels [18] and with T2D rs11061971 [19]. We found marginal association between the SNPs studied in *ADIPOQ* gene with CHD risk score, increase of HDL-c and decrease in LDL-c, suggesting that the protein expressed by this gene is involved in regulation of lipid metabolism, contributing to increase or reduction the atherogenic risk. Also, we found that the presence of CTT haplotype in *ADIPOQ* gene was associated with significant increase in adiponectin levels ($p = 0.022$).

We found that the ATA haplotype in *ADIPOR2* gene, constituted by risk alleles that confer susceptibility to MS, T (rs929434) and A (rs11061971), was marginally associated with this syndrome. Furthermore, the GTT haplotype in this gene, showed a significant effect in reducing average CHD risk score, suggesting to be a protective factor for women carrying of this haplotype. This may be because the ADIPOR2 is found mainly in the liver, and proposed as the primary site of bioactivity of adiponectin. This hormone has an effect on lipid metabolism, increases fatty acid oxidation through AMPK activation, which in turn activated by phosphorylation at the acetyl-CoA carboxylase. Adiponectin also decreases hepatic glucose production by reduction of the enzymes involved in gluconeogenesis, such as phosphoenolpyruvate carboxykinase and glucose-6-phosphatase [34].

Experiments with dominant negative mutant mice and knockout for the hepatic expression of AMPK show that this protein, especially the α2 isoform, is necessary for the activity of adiponectin decreases blood glucose [35]. In addition, adiponectin is able to activate via PPARα increasing fatty acid oxidation in the liver and muscle, this way decrease circulating triglyceride levels [36] [34].

## Conclusion

In summary, the association of adiponectin and the polymorphisms and haplotypes in the *ADIPOQ* and *ADIPOR2* genes with adiponectin levels, atherogenic risk factors or with the MS, they indicate that the expression of these genes could be involved in the development of metabolic disorders such as dyslipidemia,

hypertension, T2D, IR and CHD. The exact molecular mechanism by which these polymorphisms influence the expression of adiponectin and its biological function are not well known, given that they are in non-coding regions. However, it is possible that these polymorphisms are in linkage disequilibrium with some other functional genetic locus, which is responsible for the alteration in the production of adiponectin or its ability to polymerize, affecting its biological function, more detailed studies are needed to evaluate this effect.

**List of abbreviations**

T2D: Type-2 diabetes

IR: Insulin resistance

MS: Metabolic syndrome

CHD: Coronary heart disease

SNP: Single nucleotide polymorphism

TNF-α: Tumor necrosis factor alfa

AMPK: AMP-activated protein kinase

PPARα: Peroxisome proliferator-activated receptor alfa

**Authors' contributions**

DLAO participated in designing the genetic studies, performed the statistical analyses, most of the genotyping and drafted the manuscript. VAFT and JACP participated in acquisition of data and genotyping. MC, AVS, MEMG, LCAR and

EFA participated in designing the genetic studies and writing the manuscript. All authors read and approved the final manuscript

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**Competing interests**

The authors declare that they have no competing interests

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Table I. Sociodemographic and clinical characteristics of women with and without metabolic syndrome in southwestern Mexico

| Factor | Without MS n =237 (68.5%) | With MS n = 109 (31.5%) | p value |
|---|---|---|---|
| Age (y) | 43 (35-50) | 52 (45-56) | <0.001[1] |
| BMI (kg/m$^2$) | 26.3 (23.8-28.9) | 30.2 (26.7-33.5) | <0.001[1] |
| % Body fat | 35.4 (29.5-39) | 40.2 (36.7-44) | <0.001[1] |
| % Water | 45.1 (43-48.8) | 41.9 (39.9-44.1) | <0.001[1] |
| Waist circumference (cm) | 86 (81-93) | 94.5 (90-100) | <0.001[1] |
| Systolic BP (mmHg) | 114 (107-121) | 130 (119-137.5) | <0.001[1] |
| Diastolic BP (mmHg) | 73 (67-80) | 78.5 (72.5-86.5) | <0.001[1] |
| Glucose (mg/dl) | 78 (71-84.6) | 89.9 (79.9-107.3) | <0.001[1] |
| Total cholesterol (mg/dl) | 159.9 (140.6-182.7) | 181.9 (161.7-196.9) | <0.001[1] |
| Triglycerides (mg/dl) | 109.4 (79-140) | 166.3 (142.6-207.4) | <0.001[1] |
| HDL-c (mg/dl) | 39.5 (32.8-49.6) | 36.7 (28.9-43) | 0.001[1] |
| LDL-c (mg/dl) | 115.7 (92.7-157.1) | 125.9 (98.9-173.9) | 0.047[1] |
| CHD risk score | 9 (6-24) | 26 (12-28) | <0.001[1] |
| Adiponectin (µg/ml) | 13.5 (11.8-15.9) | 4.6 (3.5-7.3) | <0.001[1] |
| Exercise, n (%) | | | |
| No | 119 (50.2) | 53 (48.6) | 0.784[2] |
| Yes | 118 (49.8) | 56 (51.4) | |
| Smoking, n (%) | | | |
| No | 185 (78) | 86 (78.9) | 0.950[2] |
| Ex-smoker | 30 (12.7) | 14(12.8) | |
| Current smoker | 22 (9.3) | 9 (8.3) | |

The data indicate median (p25–p75), n (%).
[1] Mann Whitney´s test; [2] $X^2$ test.
CHD: coronary heart disease, HDL-c: cholesterol high density lipoprotein, LDL-c: cholesterol low density lipoproteins, BP: blood pressure

Table II. Correlation of serum adiponectin levels with clinical variables

| Factor | r* | p value |
|---|---|---|
| Age (y) | -0.2334 | 0.0036 |
| BMI (kg/m$^2$) | -0.3758 | <0.001 |
| Waist circumference (cm) | -0.4309 | <0.001 |
| Systolic BP (mmHg) | -0.2904 | 0.0003 |
| Diastolic BP (mmHg) | -0.1748 | 0.0301 |
| Glucose (mg/dl) | -0.3338 | <0.001 |
| Total cholesterol (mg/dl) | -0.1488 | 0.0656 |
| Triglycerides (mg/dl) | -0.4239 | <0.001 |
| HDL-c (mg/dl) | 0.1781 | 0.0271 |
| LDL-c (mg/dl) | -0.0363 | 0.6553 |
| CHD risk score | -0.3996 | <0.001 |

* Spearman correlation coefficient

Table III. Influence of MS and its components on adiponectin levels

| Factor | β(95%CI)* | p value |
|---|---|---|
| Metabolic syndrome | -9.1 (-10.3, -7.9) | <0.001 |
| Waist circumference (cm) | -0.14 (-0.3, -0.02) | 0.027 |
| Glucose (mg/dl) | -0.01 (-0.03, 0.003) | 0.110 |
| Triglycerides (mg/dl) | -0.01 (-0.02, -0.003) | 0.004 |
| HDL-c (mg/dl) | 0.07 (0.02, 0.13) | 0.009 |
| Systolic BP (mmHg) | -0.08 (-0.12, -0.03) | 0.002 |
| Diastolic BP (mmHg) | -0.08 (-0.15, -0.01) | 0.031 |

*Adjusted for age and BMI

Table IV. Genotype and allelic frequencies of polymorphisms in women without and with metabolic syndrome

| Factor | Without MS n (%) | With MS n (%) | p value[2] |
|---|---|---|---|
| *ADIPOQ* | | | |
| rs1501299 | | | |
| GG | 137 (57.8) | 62 (56.9) | 0.987 |
| GT | 85 (35.9) | 40 (36.7) | |
| TT | 15 (6.3) | 7 (6.4) | |
| G | 359 (75.7) | 164 (75.2) | |
| T | 115 (24.3) | 54 (24.8) | |
| rs3821799 | | | |
| CC | 69 (29.1) | 31 (28.4) | 0.637 |
| CT | 106 (44.7) | 54 (49.6) | |
| TT | 62 (26.2) | 24 (22) | |
| C | 244 (51.5) | 116 (53.2) | |
| T | 230 (48.5) | 102 (46.8) | |
| rs822395 | | | |
| AA | 141 (59.5) | 55 (50.5) | 0.278 |
| AC | 85 (35.9) | 47 (43.1) | |
| CC | 11 (4.6) | 7 (6.4) | |
| A | 367 (77.4) | 157 (72) | |
| C | 107 (22.6) | 61 (28) | |
| *ADIPOR2* | | | |
| rs767870 | | | |
| AA | 196 (82.7) | 89 (81.7) | 0.915 |
| AG | 38 (16) | 19 (17.4) | |
| GG | 3 (1.3) | 1 (0.9) | |
| A | 430 (90.7) | 197 (90.4) | |
| G | 44 (9.3) | 21 (9.6) | |
| rs929434 | | | |
| CC | 91 (38.4) | 39 (35.8) | 0.085 |
| CT | 114 (48.1) | 45 (41.3) | |
| TT | 32 (13.5) | 25 (22.9) | |
| C | 296 (62.5) | 123 (56.4) | |
| T | 178 (37.5) | 95 (43.6) | |
| rs11061971 | | | |
| TT | 113 (47.7) | 49 (45) | |
| TA | 106 (44.7) | 44 (40.4) | 0.119 |
| AA | 18 (7.6) | 16 (14.6) | |
| T | 332 (70) | 142 (65.1) | |
| A | 142 (30) | 76 (34.9) | |

[2] $X^2$ test

Table V. Association of polymorphisms with atherogenic risk factors

| SNP | Factor | Homozygous wild | Heterozygote | Homozygous variant | β (95%CI; p value) | |
|---|---|---|---|---|---|---|
| | | | | | Heterozygote | homozygous variant |
| *ADIPOQ* | | | | | | |
| rs1501299 | CHD risk score | 15.9 (9.7) | 15.9 (9.8) | 14.1 (9.8) | -0.9 (-2.2, 0.4; 0.16) | **-2.6 (-5.2, -0.1; 0.044)** |
| rs3821799 | HDL-c (mg/dl) | 37.9 (11.1) | 41.1 (12.4) | 41.3 (12.4) | **3.3 (0.3, 6.4; 0.03)** | 3.5 (0.03-7.0; 0.05) |
| rs3821799 | LDL-c (mg/dl) | 136 (50) | 132 (51) | 122 (45.3) | -5.8 (-18.1, 6.5: 0.36) | **-14.8 (-29.0, -0.7; 0.04)** |
| rs822395 | CHD risk score | 15.1 (9.6) | 16.4 (9.8) | 19.7 (10) | -0.9 (-2.2, 0.4: 0.20) | **2.9 (0.1, 5.7; 0.05)** |
| *ADIPOR2* | | | | | | |
| rs767870 | Glucose (mg/dl) | 91 (40.7) | 80.3 (17.1) | 73 (13.4) | **-10.9 (-21.4, -0.4; 0.04)** | -17.4 (-53.7, 18.9; 0.35) |
| rs767870 | CHD risk score | 16.2 (9.7) | 14.3 (9.8) | 12.3 (9.7) | **-1.9 (-3.6, -0.3; 0.02)** | -3.2 (-8.9, 2.6; 0.28) |
| rs929434 | Glucose (mg/dl) | 93.3 (47.1) | 84.2 (28.9) | 92.7 (35.1) | **-9.1 (-17.6, -0.6; 0.04)** | 0.3 (-11.2,11.7; 0.96) |
| rs929434 | Triglycerides (mg/dl) | 139.4 (66) | 132 (66) | 178 (227.3) | -6.7 (-32.0, 18.5; 0.60) | **39.1 (5.3, 73.0: 0.02)** |
| rs929434 | Adiponectin (µg/ml) | 11.5 (5.9) | 11.1 (6.1) | 9.6 (5.7) | -0.2 (-1.8, 1.3; 0.78) | **-2.1 (-4.1, -0.1; 0.04)** |
| rs11061971 | Systolic BP (mmHg) | 119 (15) | 117 (14) | 125 (18) | -1.9 (-5.0, 1.1; 0.21) | **6.1 (1.0, 11.2; 0.02)** |
| rs11061971 | Triglycerides (mg/dl) | 137 (64) | 135 (68) | 198 (290) | 0.5 (-23.6, 24.6; 0.97) | **59.6 (19.5, 100; 0.004)** |
| rs11061971 | Adiponectin (µg/ml) | 11.3 (5.7) | 11.1 (6.4) | 9 (4.8) | -0.3 (-1.8, 1.2; 0.67) | **-2.5 (-4.9, -0.1; 0.04)** |
| rs11061971 | CHD risk score | 15.8 (9.5) | 15.3 (9.7) | 18.1 (10.6) | 0.2 (-1.1, 1.5; 0.76) | **2.6 (0.4, 4.7; 0.02)** |

Data are reported as means (standard deviation).
The β coefficients were obtained using linear regression models adjusted for age and region of origin.

Table VI. Association of haplotypes in the gene *ADIPOQ* with dyslipidemia and adiponectin

| Haplotypes | | | | LDL-c ≥130mg/dl | | HDL-c ≤ 50mg/dl | | Adiponectin | | HDL-c | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **rs822395** | **rs1501299** | **rs3821799** | **Freq. (%)** | **OR (95%CI)** | **p** | **OR (95%CI)** | **P** | **β (95%CI)** | **p** | **β (95%CI)** | **p** |
| A | G | C | 35.0 | Ref. | --- | Ref. | --- | Ref. | --- | Ref. | --- |
| A | G | T | 20.6 | 1.1 (0.6-1.8) | 0.84 | 0.5 (0.3-1.0) | 0.05 | 1.4 (-0.04-2.9) | 0.058 | **2.9 (0.1-5.6)** | **0.041** |
| A | T | T | 17.5 | 0.8 (0.4-1.4) | 0.39 | 0.6 (0.3-1.1) | 0.07 | -0.5 (-2-1.1) | 0.56 | 2.7(-0.1-5.5) | 0.056 |
| C | G | C | 14.1 | 0.8 (0.4-1.8) | 0.59 | 0.5 (0.2-1.2) | 0.11 | 0.4(-1.6-2.4) | 0.72 | 1.9(-1.6-5.4) | 0.28 |
| C | G | T | 5.9 | 1.0 (0.4-2.5) | 0.96 | 0.6 (0.2-1.7) | 0.3 | -1.5 (-3.9-0.8) | 0.2 | 1.8(-3.3-6.9) | 0.49 |
| C | T | T | 4.0 | 0.6 (0.1-2.4) | 0.42 | 0.9 (0.2-4.5) | 0.88 | **3.5(0.5-6.4)** | **0.022** | 2.1(-3.8-8.0) | 0.49 |
| A | T | C | 2.5 | **4.4 (1.1-17.7)** | **0.041** | 0.5 (0.1-2.8) | 0.42 | 1.2 (-3.1-5.4) | 0.59 | 2.9(-4.6-10.3) | 0.45 |
| C | T | C | 0.4 | 2.7 (0.01-817) | 0.74 | 0.0 (-∞-+∞) | 1 | -7.9 (-18.8-3.0) | 0.16 | **23.9 (3.5-44.3)** | **0.022** |

Models adjusted for age and region of origin.