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c.+62G>A and g.-420C>G RETN Polymorphisms and the Risk of Developing Type 2 Diabetes and Obesity: Original Research on a Mexican Population and Meta-analysis

Pablo A. Montiel-Tellez[1], Adriana Nieva-Vazquez[1], Leonardo M. Porchia[2], M. Elba Gonzalez-Mejia[1], Enrique Torres-Rasgado[1], Guadalupe Ruiz-Vivanco[1,3] and Ricardo Perez-Fuentes[1,2*]

[1]Autonomous University of Puebla, 13 Sur 2901 Col. Volcanoes, C.P. 72000, Puebla, Mexico
[2]Laboratorio Research Pathophysiology of Chronic Diseases, Center for Biomedical Research East, IMSS, Km 4.5 Carretera Federal Atlixco- Metepec, C.P. 42730, Atlixco, Puebla, Mexico
[3]Tlaxcala Center for Behavioral Biology, University of Tlaxcala. Federal highway Tlaxcala - Puebla, Mexico

Abstract

Objective: To determine the association between the c.+62G>A and g.-420C>G polymorphisms and Type 2 Diabetes (T2D) or obesity susceptibility for Mexicans. Additionally, we examined their overall effect across different populations by a systematic review.

Methods: 164 Mexicans were classified as Healthy, Obese, or T2D. Genotypes were determined and associated risk for the heterozygous, homozygous, dominant, recessive, and allelic genetic models were determined by calculating the Odds Ratios (OR). For the meta-analysis, original publications that had determined RETN polymorphisms in T2D or obese subjects were searched for in PubMed, Scopus, EBSCO, Ovid, and Wiley databases until November 2015, using the search terms: T2D, obesity, RETN, and polymorphism. Pooled ORs were computed using a random-effects or fixed-effects models.

Results: For our cohort, no associations were observed between the polymorphisms and obesity or T2D. The meta-analysis indicates an increased risk of obesity among carriers of the g.-420G allele for the heterozygous and dominant models (OR=1.33 and OR=1.30, $p<0.05$, respectively). By regional assessment, Africans were associated with an elevated risk of developing T2D (OR=2.35-7.17, $p<0.05$) and obesity (OR=1.54-2.13, $p<0.05$). North Americans had an increased risk of developing obesity for the heterozygous and dominant models (OR=1.49 and OR=1.42, $p<0.05$, respectively). No associations were determined between the c.+62 polymorphism and obesity or T2D.

Conclusion: For Mexicans, none of the polymorphisms were associated with a risk of developing obesity or T2D. However, there is an increased risk of developing obesity for the whole population for subjects who carry the g.-420G allele.

Keywords: Resistin; Obesity; Polymorphisms; Type 2 Diabetes; Mexicans

Introduction

Obesity is one of the most common causes of morbidity and mortality among adults worldwide, with more than 13% of the world's adult population being obese by 2014. In Mexico, its frequency among adults was estimated to be 38.8% [1]. Obesity has been associated with the development of severe chronic diseases, such as cardiovascular heart disease [2] and Type 2 Diabetes (T2D) [3]. One supported proposed mechanism has been posited to occur through a low-grade sub-clinical inflammation state [4]. T2D represents an important cause of death among adults throughout the world. Its global prevalence is estimated to be 9% among subjects aged over 18 years old, whereas in Mexico it was 9.2% in 2012 [1]. Diabetes is considered to be a polygenic disease. Many single nucleotide polymorphisms (SNPs), including those in cytokine genes such as TNF-α [5], IL-6 [6], IL-10 [7], adiponectin [7], and resistin [8,9] have been reported to increase the risk of developing T2D and obesity.

RETN encodes for resistin, a cysteine-rich C-terminal domain polypeptide secreted in humans by monocytes, macrophages, and adipocytes [10-12]. This cytokine has been proposed as a link between obesity and T2D, and has been involved in inflammation through the increase of TNF-α, IL-6 and IL-12 [13,14]. Furthermore, it has been demonstrated that adipocytes and macrophages treated with resistin enhance lipid accumulation [15-17], whereas skeletal muscle cells show a decreased fatty acid uptake under the same condition, which may further lead to lipotoxicity and insulin resistance [18]. Two polymorphisms of RETN, c.+62G>A and g.-420C>G, have been shown to impair resistin expression [19-22].

Many groups have examined the association between the c.+62G>A and g.-420C>G polymorphisms and the risk of developing either obesity or T2D. Solaleh and Motawi found in Asians and Africans [9,8], an augmented risk of developing T2D was associated with the g.-420C>G polymorphism, whereas Chi and Chen found in Asia and Northern America no risk [23,24]. In the same manner, in Africans there was a positive association between obesity and the g.-420C>G polymorphism [25,26]; whereas, Apasalamy failed to observe any change in risk [19]. Therefore, the exact effect the g.-420C>G polymorphism has toward T2D and obesity development remains inconsistent, especially in regard to ethnicity. Furthermore, in Latinos, only one study has been conducted which explored the association between the c.+62G>A and adiposity [27], suggesting the presence of this mutation was associated

***Corresponding author:** Ricardo Pérez-Fuentes, Facultad de Medicina, Benemérita Universidad Autónoma de Puebla, 13 Sur 2901 Col. Volcanes, C.P. 72000, Puebla, Pue, México, Tel: +52 (222) 244 44 122; E-Mail: rycardoperez@hotmail.com

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with overweight. The aim of the present study was to analyze whether there is an increased risk of developing obesity or T2D among Mexican adults carrying the c.+62G>A and g.-420C>G polymorphisms. Moreover, we performed a meta-analysis to analyzed the overall effect of these polymorphisms have on obesity and T2D development across different populations.

Materials and methods

Subjects

A cross-sectional study was designed, which included 164 unrelated Mexican subjects from the City of Puebla, Mexico, whose ages ranged between 18 and 70 years. The subjects were outpatients from IMSS Clinic 2 and were recruited between January 2010 and December 2013. Healthy subjects, as well as obese and diabetic subjects, were asked to participate. Subjects were excluded from the study if it was suspected that they had any acute or chronic illness that would interfere with the analysis, or if they met the criteria to be classified as pre-diabetic or overweight (BMI: 25-30 kg/m^2). All the healthy and obese subjects were already used in a previous report [28]. The protocol was approved by the Scientific Research Committee of the Mexican Social Security Institute and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from each subject after explanation of the nature of the study.

Clinical characterization

Subjects were clinically evaluated according to a standardized questionnaire including their personal medical history. With the subjects in fasting conditions, wearing light clothing and without shoes, their height (m) and weight (Kg) were measured using a body composition analyzer (Tanita, Itabashi-Ku, Tokyo). BMI was calculated as weight/height^2 (Kg/m^2). Obesity was defined according with the International Diabetes Federation (BMI ≥30 kg/m$_2$) and Diabetes according to the America Diabetes Association criteria (Fasting Plasma Glucose: ≥126 mg/dL and/or 2-hour post-prandial glucose: ≥200 mg/dL).

Biochemical assays

Blood samples were drawn from the antecubital vein following a 10-12 h overnight fast and collected into a Vacutainer® Plus plastic sterile tube with BD Hemogard™ closure containing sodium fluoride and potassium oxalate (Catalog #367925, BD Mexico City, Mexico). Subjects also underwent a second venipuncture 2 hours after drinking a glucose-containing solution (75 g) to assess post-prandial glycemic control. The samples were kept in serum clot activator tubes at room temperature for 20 minutes. The serum fraction was then recovered and frozen at -20°C until use. Samples were used for the following endpoints: fasting plasma glucose and post-prandial glucose test. Glucose was determined using the enzymatic method/spectrophotometric glucose oxidation.

Genotyping

Blood samples for DNA extraction were stored in EDTA-containing tubes. DNA was isolated from peripheral blood leucocytes using the salting out method [29] and the DTAB-CTAB method [30]. Resistin genotypes were determined using PCR-RFLP (GeneAmp PCR System 9700, Applied Biosystems, Foster City, CA). The sequence of the RETN promoter and 3'UTR were obtained from the Eukaryotic Promoter Database (Swiss Institute of Bioinformatics, Lausanne, Switzerland), and primers were designed using the FastPCR software (Helsinki, Finland).

For the g.-420C>G polymorphism, forward and reverse primers were 5'- TGTCATTCTCACCCAGAGACA-3' and 3 -'GATTTGGTTAGCTGAGCCCA-5', respectively, which produced a 533 bp PCR product. The PCR products were further digested overnight using the *Bb*SI restriction enzyme (Catalog #R0539S, New England BioLabs Inc.). The digested products were then separated in 6% polyacrylamide gel and stained with silver nitrate. Digestion of the C allele yielded two fragments (327 and 206 bp), whereas the G allele produced a single fragment (533 bp). Thus, wild type homozygous produced two bands, those carrying the polymorphism produced a single band, and heterozygous produced three bands.

The forward and reverse primers for the c.+62G>A polymorphism were 5'-AGAGTCCACGCTCCTGTGTT-3' and 3'-CGACCTTTATTTGGACCTCTAC-5', respectively, which produced a 249 bp PCR product. The PCR products were digested overnight using *Bse*RI restriction enzyme (Catalog #R0581S, New England BioLabs Inc.). The A allele, after digestion, would produce two fragments (238 and 11 bp), while the G allele produce a single fragment (249 bp). Electrophoresis patterns were as follows: wild type homozygous produced a single band, mutant homozygous produced two bands, and heterozygous produced three bands.

Publication Search

Literature was searched using PubMed, Scopus, EBSCO, Ovid and Wiley databases, until November 2015, for case-control studies conducted on humans that have determined RETN polymorphisms in diabetic or obese subjects. The keywords and related terms used were: *Type 2 Diabetes* or *obesity, RETN,* and *single nucleotide polymorphism*. Manual search of the references lists of the retrieved articles was performed to identify more studies.

Inclusion and exclusion criteria

Articles were eligible if they met all of the following criteria: *i*) Explored the association between either T2D or Obesity (BMI ≥30 Kg/m^2) and RETN polymorphisms, *ii*) were case-control studies, and *iii*) reported genotype frequencies, as well as odds ratios estimates with 95% confidence intervals or provided sufficient data to calculate them. Studies were excluded on the basis of the following criteria: *i*) presented data as an editorial, a review or a meeting abstract, *ii*) did not provide sufficient data, *iii*) data were presented in another more representative study from the same research group, or *iv)* was not written in English or Spanish. Two authors determined if each study was to be included. Afterwards, only studies focusing on RETN polymorphisms g.-420C>G and c.+62A>G were considered.

Data extraction

Two authors extracted the data independently. If there was disagreement, a third author assessed the study in question. If a single sample was believed to be used in multiple reports, these were assessed to determine which one was the most representative, or the corresponding author was contacted to resolve the issue. The data collected were: first author's name, publication year, geographical region, T2D/obesity, T2D definition, genotyping method, source of controls, distribution of genotypes among the cases and controls, as well as the total number of subjects.

Statistical analysis

The normality of the data was assessed by the Kolmogorov-Smirnov test. Continuous variables presented normal distribution and variance homogeneity, therefore they were analyzed using the one-way ANOVA test; the Bonferroni post hoc test was performed to identify between-

group differences. Allele frequencies were computed from genotype frequencies. Fisher's exact test was used to search for differences in allele and genotype frequencies among groups. Deviation from Hardy-Weinberg Equilibrium (HWE) was assessed using the ψ^2-test for the controls.

For the meta-analysis, the HWE for each study was determined by the ψ^2-test for the controls. The crude odds ratio (OR) and the 95% confidence interval (95% CI) were calculated for each study and used to assess the level of association between the mutation and T2D or obesity. The pooled ORs were assessed for the following genetic models: homozygous (22 versus 11), heterozygous (12 versus 11), dominant (12 + 22 versus 11), recessive (22 versus 12 + 11), and allelic (2 versus 1); where 1 corresponds to C and A, and 2 corresponds to G and G for the g.-420C>G and c.+62A>G mutations, respectively. Heterogeneity was determined using the Cochran ψ_2 -based Q-test, and its degree was assessed by the I^2 value (inconsistency index). If the Q-test p-value was <0.10 or the I^2 value was >50%, the pooled ORs were determined using the random-effects model (DerSimmonian-Laird method) [31], otherwise the fixed-effects model (Mantel-Haenszel method) [32] was selected. The stability and sensitivity of the results were assessed by removing one study at a time and re-calculating the pooled ORs. Publication bias was evaluated by the Begg-Mazumdar's adjusted rank correlation asymmetry test (Kendall's tau) [33] and the Egger regression asymmetry test [34].

Statistical analyses were performed using either Statistical Package for the Social Sciences software for Windows, version 22 (SPSS, Chicago, IL), Review Manager version 5.3 (Copenhagen, DK) or StatsDirect version 3.0.147 (Cheshire, UK). Results were expressed as mean ± standard deviation, unless noted otherwise. *P*-values <0.05 (two-tailed) were considered statistically significant.

Results

Subjects' characterization

Our cohort consisted of 164 unrelated Mexican adults (45 males and 119 females). Subjects were divided into three groups according to their anthropometric and glycemic status: Control (n=49), Obese (n=70) and T2D (n=45). The anthropometric and biochemical characteristics of the three groups are presented in Table 1. Fifteen subjects had a previous diagnosis of T2D, whereas thirty of them were newly diagnosed during the protocol. The Obese group showed higher anthropometric measures, as well as fasting plasma glucose, compared with the control group (p<0.05). T2D subjects were older than those in the other two groups, and presented higher anthropometric measures than controls, but lower than the obese subjects (p<0.05). Both fasting plasma glucose and 2-hour prandial glucose levels were statistically higher in the T2D group than in the others (p<0.05).

Lack of association of g.-420C>G or c.+62A>G polymorphisms with susceptibility to T2D or Obesity

Genotype distribution, allele frequencies, and ORs for the g.-420C>G and c.+62A>G mutations are presented in Table 2. Genotype distribution for the controls was in accordance with the HWE. None of the genetic models showed any significant increase in the risk of developing T2D or Obesity in the presence of the either polymorphism.

Characteristics of the studies from literature review

Three hundred forty-seven studies were retrieved from searching the databases and from reviewing the studies' references lists. Two hundred ninety-five studies were excluded because they did not focus on diabetes or Obesity and RETN, focused on animals or cell lines, or were not original research articles. The remaining fifty-two studies were evaluated extensively. Five studies were not written in English or Spanish, six lacked sufficient information, seven were not case-control studies, two were duplicate studies, three considered different BMI cutoffs for obesity, and one focused on children and were therefore excluded (Figure 1). From the remaining twenty-eight studies, eighteen focused on the g.-420C>G polymorphism [8,9,19,21,23-26,35-44] and four on the c.+62A>G polymorphism [22,25,45,46]. Our current study was also considered for the meta-analysis. For the g.-420C>G polymorphism, the sample for the T2D analysis of the consisted of 8986 cases and 13288 controls, while there were 1240 cases and 2387 controls for the obesity analysis. For the c.+62A>G polymorphism, the sample for the T2D analysis consisted of 1883 cases and 1384 controls and for Obesity there were 230 cases and 215 controls. Deviations from HWE were found in five studies for the g.-420C>G polymorphism [8,25,35,38,39,]. However, analyses removing these populations did not show a significant variation; therefore they were included in the meta-analysis. Detailed characteristics of the studies are listed in Table 3.

Meta-analysis of the association of g.-420C>G or c.+62A>G with Obesity and T2D

Overall, this meta-analysis showed an increased risk of developing Obesity associated with the g.-420C>G polymorphism for the heterozygous and dominant genetic models (OR=1.33, 95%CI: 1.01-1.75, $p_{\text{heterogeneity}}$=0.01, I^2=64%, and OR=1.30, 95%CI: 1.00-1.68, $p_{\text{heterogeneity}}$=0.01, I^2=64%, respectively; Figure 2 and Table 4). However, when stratifying by geographic region, the association was true for the African (OR=1.54-2.13, p<0.05) and North American regions (OR=1.42-1.49, p<0.05, Table 5). The African region was also associated with an elevated risk of developing T2D (OR=2.35-7.17, p<0.05, Table 5). No other associations between the g.-420C>G polymorphism and the risk of developing T2D was demonstrated for other regions (Table 4). None of the genetic models showed an association between the c.+62A>G mutation and the risk of developing Obesity or T2D for the overall (Figure 2 and Table 4) and regional analysis (data not shown). See supplementary information for all Forest plots.

Test for sensitivity and publication bias

Publication bias was assessed by examining Begg's funnel plot, calculating the Begg-Mazumdar´s test and Egger's asymmetry test. The funnel plot did not indicate any major asymmetry (Figure 3). Furthermore, neither Begg-Mazumdar´s nor Egger's test did indicate any significant bias for any genetic model (for dominant model: Begg-Mazumdar's Kendall's tau= 0.017, p=0.96; Egger: bias=-0.01, p=0.98). Heterozygous and dominant genetic models for the analysis of the association between the g.-420C>G mutation and Obesity were sensitive to the removal of either Engert (Northern American population), Boumaiza or El-Shal studies, resulting in the loss of significance (CG *vs* CC: OR=1.30, 95%CI: 0.94-1.80; OR=1.18, 95%CI: 0.96-1.46 and OR=1.28, 95%CI: 0.95-1.74, respectively). For the analysis of the association between the c.+62G>A mutation and T2D, heterozygous, dominant and allelic models showed sensitivity to the removal of Jiang's study, resulting in a decreased risk of developing the condition (GA *vs* GG: OR=0.63, 95%CI: 0.51-0.78; GA+AA *vs* GG: OR=0.63, 95%CI: 0.51-0.78; A *vs* G: OR=0.66, 95%CI: 0.55-0.80). None of the other studies had a significant effect on the ORs for either polymorphisms and condition.

Discussion

T2D is a leading cause of morbidity and mortality among adults

Variable	Control	Obese	T2D [a]
	(n=49)	(n=70)	(n=45)
Gender (F/M)	38/11	48/22	33/12
Age (years)	34.6 ± 9.9	37.5 ± 10.4	53.0 ± 6.5 *,†
Height (m)	1.6 ± 0.1	1.6 ± 0.6	1.6 ± 0.1
Weight (Kg)	56.6 ± 7.2	86.5 ± 12.4 *	64.5 ± 10.8 *,†
Body-Mass index (Kg/m^2)	22.8 ± 1.6	33.6 ± 3.1 *	26.7 ± 3.7 *,†
Fasting Plasma Glucose (mg/dL)	87.5 ± 6.1	93.1 ± 6.8 *	108.5 ± 19.0 *,†
Post-prandial Glucose test (mg/dL)	97.2 ± 2.0	108.7 ± 17.0	165.0 ± 69.0 *,†

Results are expressed as mean ± standard deviation. Data were analyzed using the one-way ANOVA test. Between-group differences were identified through the post-hoc Bonferroni test. * vs C, † vs OB. $p < 0.05$.[a] 15 subjects did not undergo the Post-prandial Glucose test because they already had a previous diagnosis of T2D.

Table 1: Characterization of the population by groups.

Polymorphism	Control	Obese	T2D	HWE, *P*[a]	Genetic model	T2D			Obesity		
	n (freq)	n (freq)	n (freq)			OR	95% CI	P[b]	OR	95% CI	P[b]
c.-420C>G				0.06							
C/C	37 (0.80)	56 (0.80)	37 (0.82)		**C/G vs C/C**	1	0.32-3.13	1	1.13	0.41-3.14	0.81
C/G	7 (0.15)	12 (0.17)	7 (0.16)		**G/G vs C/C**	0.5	0.04-5.76	0.58	0.66	0.09-4.90	0.69
G/G	2 (0.04)	2 (0.03)	1 (0.02)		**C/G+G/G vs C/C**	0.89	0.31-2.56	0.83	1.03	0.40-2.62	0.95
C	81 (0.88)	124 (0.89)	81 (0.90)		**G/G vs C/ G+C/C**	0.5	0.04-5.72	0.58	0.65	0.09-4.76	0.67
G	11 (0.12)	16 (0.11)	9 (0.10)		**G vs C**	0.82	0.32-2.08	0.67	0.95	0.42-2.15	0.9
g.+62G>A				0.052							
G/G	41 (0.89)	63 (0.90)	39 (0.87)		**G/A vs G/G**	1.31	0.33-5.26	0.7	0.81	0.21-3.21	0.77
G/A	4 (0.09)	5 (0.07)	5 (0.11)		**A/A vs G/G**	1.05	0.06-17.40	0.97	1.3	0.11-14.82	0.83
A/A	1 (0.02)	2 (0.03)	1 (0.02)		**G/A+A/A vs G/G**	1.26	0.36-4.47	0.72	0.91	0.27-3.07	0.88
G	86 (0.93)	131 (0.94)	83 (0.92)		**A/A vs G/ A+G/G**	1.02	0.06-16.87	0.99	1.32	0.12-15.03	0.82
A	6 (0.07)	9 (0.06)	7 (0.08)		**G vs A**	1.21	0.39-3.75	0.74	0.99	0.34-2.87	0.98

Abbreviations: T2D, Type 2 Diabetes; HWE, Hardy-Weinberg equilibrium (only controls); OR, odds ratio; CI, confidence interval; freq, frequency.
c.-420C>G: C= wild type allele, G= minor allele. G.+62G>A: G= wild type allele, A= minor allele.
a calculated using the chi-squared test.
b calculated using logistic regression.

Table 2: Genotype distribution and allele frequencies by group.

worldwide, and obesity has been demonstrated to be a major risk factor for its development [47]. Both conditions can feature a low-grade inflammation state. Since many cytokines have proved to play a role in this phenomenon [48-51], the RETN gene was examined. Two mutations of RETN, g.-420C>G and c.+62G>A, altered resistin expression in previous reports [19-21], however, their effect on augmenting the risk of developing obesity or T2D remains inconclusive. Here, we demonstrate that only the g.-420C>G polymorphisms augments the risk of developing obesity.

Only one study has been conducted on Mexican subjects that indirectly explored the association between the c.+62G>A mutation and overweight [27]. They determined that the A allele was associated with a low BMI, as well as with low resistin levels. A study in a Chinese

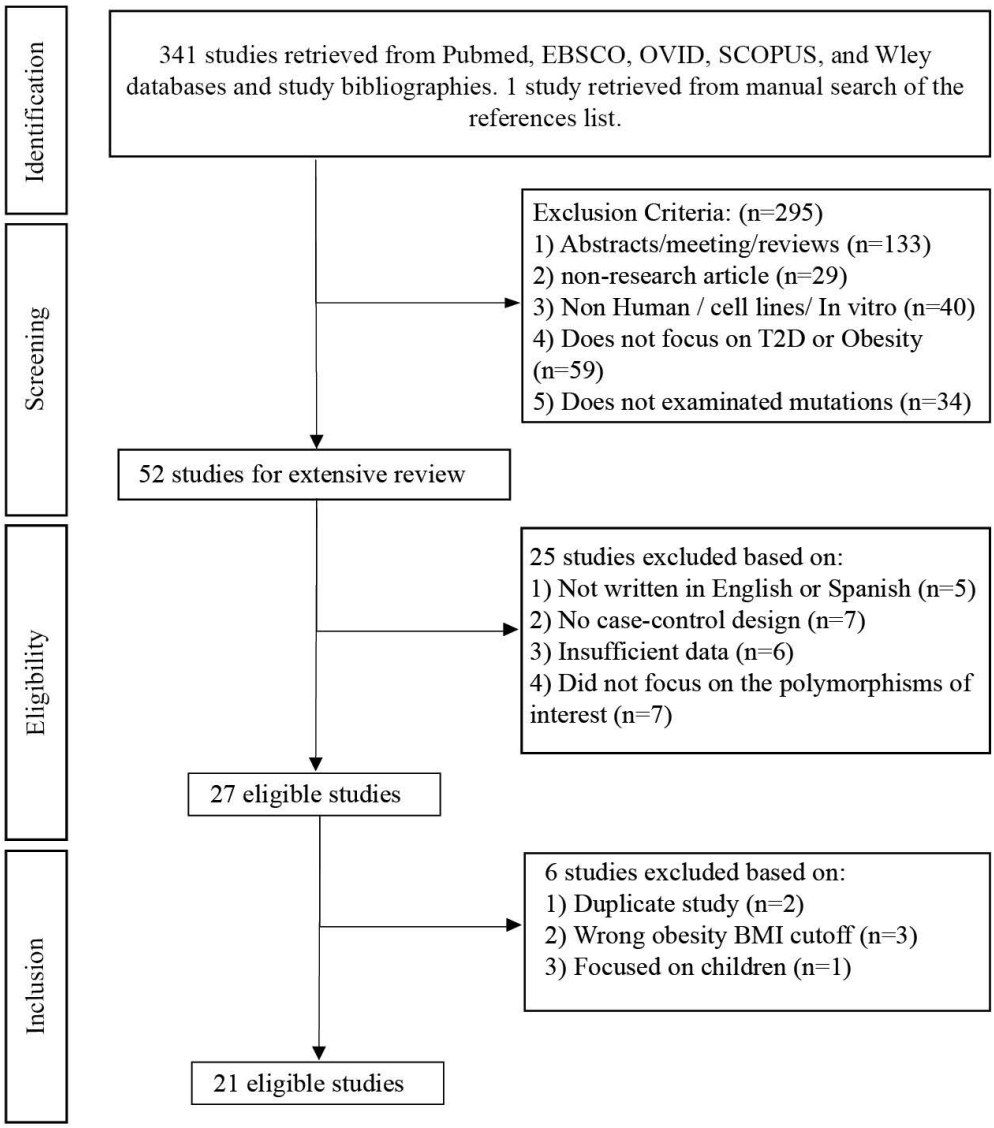

Figure 1: Flow chart for literature review of studies to be included in the meta-analysis.

population found a similar association between the A allele and a decreased risk of developing T2D [22]. In our population, however, there were no differences in either genotype distribution or allelic frequencies for both polymorphisms examined between the Control group and the obesity or the T2D groups; therefore, no associations were found in any of the genetic models. These results were in accordance with previous reports for Asians, Northern Americans, and Europe [21,23,24,36,37,39-43,45,46]. However, two studies, conducted in Asians [8] and Africans [9] population have shown an increased risk of developing T2D related to the g.-420C>G mutation. Furthermore, two other African studies detected a 2.22 and 3.06-fold increased risks of developing obesity among carriers of the g.-420G allele [25,26].

Due to the inconsistency of the data between ethnicities and because it has been demonstrated that some mutations have an effect only under certain ethnic genetic influences, this meta-analysis was performed. To our knowledge, this is the first meta-analysis which examined the effect of the c.+62G>A polymorphism on obesity or T2D. Here, we reported that the c.+62G>A polymorphism showed no association in any of the genetic models for obesity or T2D. Nor was there any association between the g.-420C>G mutation and the risk of developing T2D. The meta-analysis demonstrated, however, an increased risk of developing Obesity among carriers of the g.-420C>G allele. Moreover, when stratifying by geographic region, the association was true for the African and North American regions. It is possible, therefore, that subjects with an African ancestry component might also show an elevated risk of developing obesity when they carry the mutated allele. Further investigations are required to assess

Disease	Author, Year	Region	Case [a]	Controls [a]	HWE, P[b]	Ref.
			11 / 12 / 22	**11 / 12 / 22**		
g.-420C>G						
T2D	Bouchard, 2004	NA	22 / 17 / 3	337 / 256 / 90	<0.001	[35]
	Cauchi, 2008	EU	1365 / 1159 / 257	2071 / 1779 / 393	0.697	[36]
	Chen, 2010	NA	246 / 225 / 49	245 / 223 / 50	0.943	[23]
	Chi, 2009	AS	111 / 159 / 48	138 / 178 / 54	0.781	[24]
	Cho, 2003	AS	194 / 163 / 54	89 / 63 / 21	0.068	[37]
	Emamgholipur, 2009	AS	23 / 16 / 8	16 / 41 / 9	0.037	[8]
	Engert, 2002	EU	238 / 170 / 44	236 / 156 / 41	0.046	[38]
	Engert, 2002	NA	90 / 78 / 11	212 / 169 / 39	0.528	[38]
	Hishida, 2013	AS	76 / 74 / 11	1062 / 1087 / 341	0.019	[39]
	Kunnari, 2004	EU	151 / 85 / 18	266 / 197 / 29	0.343	[40]
	Lau, 2010	AS	147 / 220 / 60	70 / 104 / 34	0.656	[41]
	Ma, 2002	NA	148 / 128 / 24	140 / 134 / 24	0.301	[42]
	Motawi,2014	AF	21 / 35 / 34	31 / 22 / 7	0.325	[9]
	Ochi, 2007	AS	1169 / 1144 / 297	1080 / 1123 / 299	0.787	[43]
	Tsukahara, 2008	AS	155 / 147 / 47	116 / 130 / 40	0.712	[21]
	Current study	CA	37 / 7 / 1	37 / 7 / 2	0.06	----
Obesity	Apasalamy, 2015	AS	34 / 85 / 43	101 / 233 / 135	0.98	[19]
	Beckers, 2007	EU	111 / 104 / 20	255 / 238 / 48	0.474	[44]
	Boumaiza, 2012	AF	40 / 93 / 27	72 / 63 / 34	0.005	[25]
	El-Shal, 2012	AF	50 / 66 / 29	79 / 61 / 15	0.524	[26]
	Engert, 2002	EU	117 / 77 / 20	357 / 249 / 65	0.029	[38]
	Engert, 2002	NA	116 / 121 / 17	186 / 126 / 24	0.675	[38]
	Current study	CA	56 / 12 / 2	37 / 7 / 2	0.06	----

c.+62G>A						
T2D	Gouni, 2005	EU	360 / 23 / 1	400 / 34 / 0	0.396	[45]
	Jiang, 2013	AS	256 / 87 / 9	122 / 35 / 4	0.442	[46]
	Tan, 2002	AS	920 / 176 / 6	558 / 178 / 7	0.078	[22]
	Current data	CA	39 / 5 / 1	41 / 4 / 1	0.052	----
Obesity	Boumaiza, 2012	AF	132 / 28 / 0	147 / 20 / 2	0.181	[25]
	Current data	CA	63 / 5 / 2	41 / 4 / 1	0.052	----

Abbreviations: T2D, Type 2 Diabetes; HWE, Hardy-Weinberg Equilibrium; AF, Africa; AS, Asia; CA, Central America; EU, Europe; and NA, Northern America.
[a] For g.-420C>G: 1 = wild type allele (C), 2 = minor allele (G). For c.+62G>A, 1 = wild type allele (G), 2 = minor allele (A).
[b] p-value, calculated by chi-squared test.

Table 3: Characteristics of the studies included in the meta-analysis for g.-420C>G and c.+62G>A polymorphisms of the RETN promoter.

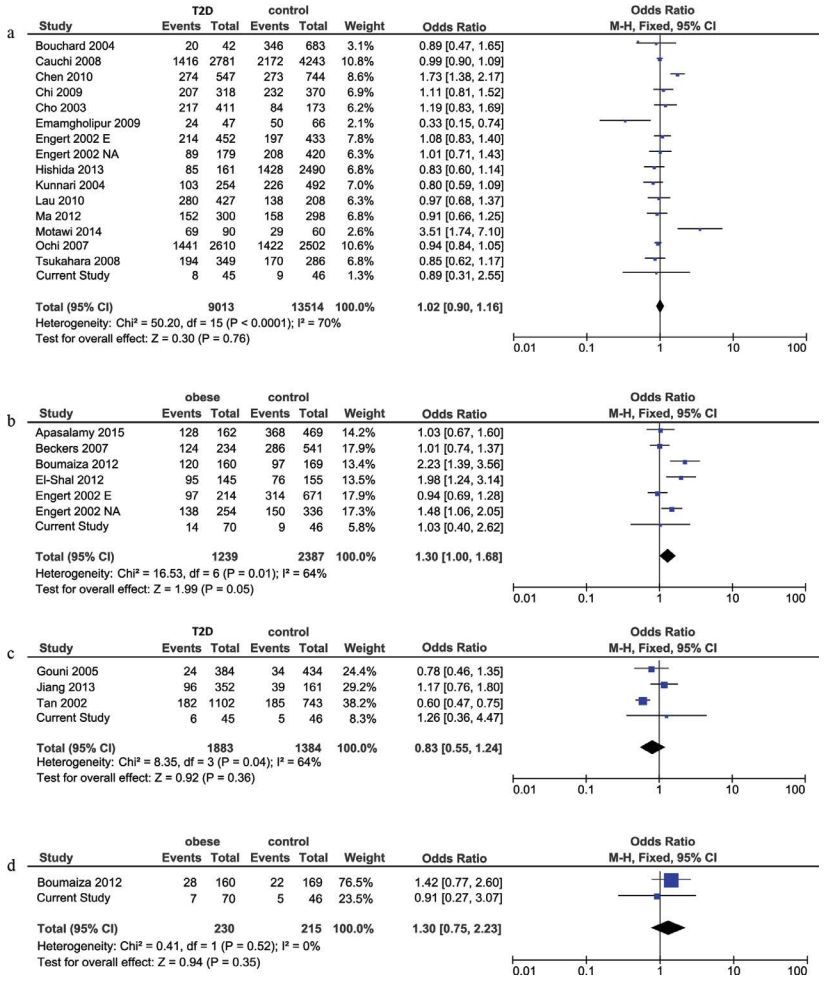

Figure 2: The risk associated developing obesity or Type 2 Diabetes (T2D) with the RETN g.-420C>G or c.+62G>A polymorphisms. Forest Plots were constructed for the five genetic models (data shown is for the dominant model) to examined the association between a) the RETN g.-420C>G polymorphism and T2D, b) the RETN g.-420C>G polymorphism and obesity, c) the RETN c.+62G>A polymorphism and T2D, and d) the RETN c.+62G>A polymorphism and obesity.

				Heterogeneity			Publication Bias	
Polymorphism	**Disease**	**Genetic Model**	**OR (95% CI)** [a]	**Q-test** [b]	**I²-test**	**Model** [c]	**Begg's** [d]	**Egger's** [e]
g.-420C>G	T2D							
		CG v CC	0.97 (0.92-1.03)	0.19	24%	FE	0.17	0.19
		GG v CC	0.96 (0.81-1.13)	0.04	43%	RE	0.2	0.96
		CG + GG v CC	1.02 (0.90-1.16)	<0.01	70%	RE	0.76	0.82
		GG v CG +CC	0.97 (0.88-1.06)	0.12	31%	FE	0.69	0.99
		C v G	0.98 (0.90-1.06)	<0.01	54%	RE	0.31	0.85
	Obesity							
		CG v CC	1.33 (1.01-1.75) *	0.01	64%	RE	0.24	0.43
		GG v CC	1.17 (0.93-1.49)	0.16	36%	FE	0.07	0.77
		CG + GG v CC	1.30 (1.00-1.68) *	0.01	64%	RE	0.14	0.46
		GG v CG +CC	1.00 (0.81-1.24)	0.3	18%	FE	0.99	0.78
		C v G	1.15 (0.97-1.36)	<0.05	57%	RE	0.14	0.56
c.+62G>A	T2D							
		CG v CC	0.82 (0.55-1.22)	0.05	62%	RE	0.75	0.31
		GG v CC	0.83 (0.40-1.73)	0.65	0%	FE	0.33	0.31
		CG + GG v CC	0.83 (0.55-1.24)	0.04	64%	RE	0.75	0.3
		GG v CG +CC	0.85 (0.41-1.78)	0.72	0%	FE	0.33	0.28
		C v G	0.84 (0.58-1.20)	0.05	62%	RE	0.33	0.32
	Obesity							
		CG v CC	1.40 (0.79-2.46)	0.4	0%	FE	N/A	N/A
		GG v CC	0.58 (0.11-3.20)	0.37	0%	FE	N/A	N/A
		CG + GG v CC	1.30 (0.75-2.23)	0.52	0%	FE	N/A	N/A
		GG v CG +CC	0.57 (0.11-3.10)	0.35	0%	FE	N/A	N/A
		C v G	1.19 (0.72-1.97)	0.69	0%	FE	N/A	N/A

[a] Significant associations are indicated by * (p-value <0.05)
[b] p-value was calculated by Cochran ψ²-based Q-test using RevMan v5.3. * p<0.05
[c] FE: Fixed-effects model (Q-tests p-value ≥0.10, I²-test <50%) and RE: Random-effects model (Q-tests p-value <0.10, I²-test ≥50%)
[d] Begg-Mazumdar test was used to calculate publication bias. Results are given as Kendall's tau and p-value (any less than 0.1 was consider significant for publication bias)
[e] Egger's test was used to calculate publication bias. Results are given as a p-value (any less than 0.1 was consider significant for publication bias).

Table 4: RETN polymorphism association with the development of Obesity and Type 2 Diabetes for the overall population.

this association among Mexicans from regions where there is a more prominent African ancestry component, like in Guerrero state [52].

Two previous meta-analyses examined the overall effect of the g.-420C>G mutation. Wen et al. demonstrated that there was no association between the polymorphism and the risk of T2D; however, it only considered European, Asian and Northern American populations, and not African or Latin Americans [53]. Yu et al also demonstrated no association between the polymorphism and obesity. It included two populations from Europe, one from Northern America and one from Brazil (European descendants), but none from Latin America or Africa [54]. Discrepancies between these results and ours might be due to fact that they did not considered African populations, which here we demonstrate are highly susceptible.

Our study has at least three limitations. First, our subjects were not separated by gender. Some authors have found differences in anthropometric measures within male and female carriers of the g.-420G allele [35,38,55,56]. Second, our population was formed mainly of subjects from Central Mexico, which have a predominant European ancestry component. As mentioned above, Mexico is highly diverse country with many different composition of European, African, and Native American. Third, for the meta-analysis, we used crude ORs and non-adjusted ORs. Adjusting the ORs can affect the ORs by a few tenths.

Conclusions

In summary, neither g.-420C>G nor c.+62G>A are associated with T2D with the overall population. Only the g.-420C>G polymorphism was associated with an increased risk of developing obesity. This effect was associated with African and North Americans. Whether subjects with an African ancestry component show the same susceptibility pattern has yet to be investigated.

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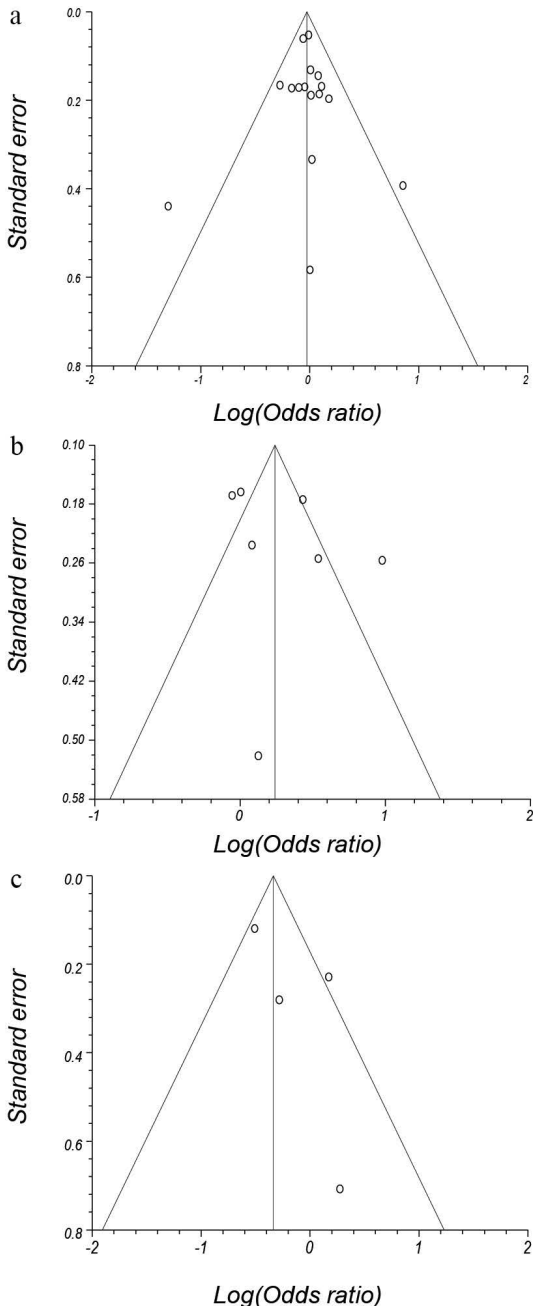

Figure 3: Begg's funnel plot for publication bias test. For the RETN g.-420C>G polymorphism, no detrimental publication bias was observed for the Type 2 Diabetes analysis (a) and the obesity analysis (b). As well for the RETN c.+62G>A polymorphism, no detrimental publication bias was observed for the the Type 2 Diabetes analysis (c). Due to the sample size, no publication bias can be determined for the c.+62G>A polymorphism and obesity analysis. Each point represents a separate study for the indicated association. Funnel plots are for the dominant model.

					Heterogeneity		
Disease	**Genetic Model**	**Ethnicity**	**n** [a]	**OR (95% CI)** [b]	**Q-test** [c]	**I²-test**	**Model** [d]
T2D							
	CG v CC	NA	5	1.00 (0.84-1.18)	0.97	0%	FE
		EU	3	0.98 (0.89-1.07)	0.24	30%	FE
		AS	7	0.95 (0.87-1.04)	0.09	45%	FE
		AF	1	2.35 (1.09-5.07) *	N/A	N/A	N/A
	GG v CC	NA	5	0.85 (0.63-1.15)	0.77	0%	FE
		EU	3	1.01 (0.86-1.18)	0.93	0%	FE
		AS	7	0.89 (0.78-1.03)	0.36	0%	FE

		AF	1	7.17 (2.68-19.18) *	N/A	N/A	N/A
	CG + GG v CC	NA	5	1.11 (0.78-1.57)	<0.01	73%	RE
		EU	3	0.98 (0.90-1.07)	0.34	7%	FE
		AS	7	0.94 (0.86-1.02)	0.12	40%	FE
		AF	1	3.51 (1.74-7.10) *	N/A	N/A	N/A
	GG v CG +CC	NA	5	0.85 (0.64-1.11)	0.69	0%	FE
		EU	3	1.01 (0.87-1.18)	0.82	0%	FE
		AS	7	0.92 (0.81-1.05)	0.41	2%	FE
		AF	1	4.60 (1.88-11.26) *	N/A	N/A	N/A
	C v G	NA	5	0.95 (0.84-1.08)	0.94	0%	FE
		EU	3	0.99 (0.93-1.06)	0.59	0%	FE
		AS	7	0.95 (0.89-1.01)	0.28	20%	FE
		AF	1	3.12 (1.91-5.09) *	N/A	N/A	N/A
Obesity							
	CG v CC	NA	2	1.49 (1.08-2.08) *	0.58	0%	FE
		EU	2	0.97 (0.77-1.23)	0.79	0%	FE
		AS	1	1.08 (0.68-1.72)	N/A	N/A	N/A
		AF	2	2.13 (1.38-2.81) *	0.22	33%	FE
	GG v CC	NA	2	1.08 (0.57-2.82)	0.16	36%	FE
		EU	2	0.95 (0.64-1.40)	0.96	0%	FE
		AS	1	0.95 (0.56-1.59)	N/A	N/A	N/A
		AF	2	2.01 (1.25-3.21) *	0.12	59%	FE
	CG + GG v CC	NA	2	1.42 (1.04-1.93) *	0.47	0%	FE
		EU	2	0.97 (0.78-1.21)	0.77	0%	FE
		AS	1	1.03 (0.67-1.80)	N/A	N/A	N/A
		AF	2	2.10 (1.51-2.92) *	0.72	0%	FE
	GG v CG +CC	NA	2	0.90 (0.49-1.66)	0.73	0%	FE
		EU	2	0.96 (0.66-1.40)	0.99	0%	FE
		AS	1	0.89 (0.60-1.34)	N/A	N/A	N/A
		AF	2	1.35 (0.48-3.82)	0.02	82%	RE
	C v G	NA	2	1.23 (0.96-1.56)	0.52	0%	FE
		EU	2	0.97 (0.82-1.15)	0.84	0%	FE
		AS	1	0.97 (0.75-1.24)	N/A	N/A	N/A
		AF	2	1.54 (1.16-2.05) *	0.21	36%	FE

[a] # of studies
[b] Significant associations are indicated by * (p-value <0.05)
[c] p-value was calculated by Cochran ψ^2-based Q-test using RevMan v5.3. * p<0.05.
[d] FE: Fixed-effects model (Q-tests p-value ≥0.10, I^2-test <50%) and RE: Random-effects model (Q-tests p-value <0.10, I^2-test ≥50%)

Table 5: RETN g.-420C>G polymorphism association with the development of Obesity and Type 2 Diabetes by geographical region.

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Author disclosure statement

The authors report that there are no competing financial interests.

References

1. Medina C, Janssen I, Campos I, Barquera S (2013) Physical inactivity prevalence and trends among Mexican adults: results from the National Health and Nutrition Survey (ENSANUT) 2006 and 2012. BMC Public Health 13: 1063.
2. Mathew B, Francis L, Kayalar A, Cone J (2008) Obesity: effects on cardiovascular disease and its diagnosis. J Am Board Fam Med 21: 562-568.
3. Kodama S, Horikawa C, Fujihara K, Heianza Y, Hirasawa R, et al. (2012) Comparisons of the strength of associations with future type 2 diabetes risk among anthropometric obesity indicators, including waist-to-height ratio: a meta-analysis. Am J Epidemiol 176: 959-969.
4. van Greevenbroek MM, Schalkwijk CG, Stehouwer CD (2013) Obesity-associated low-grade inflammation in type 2 diabetes mellitus: causes and consequences. Neth J Med 71: 174-187.
5. Saxena M, Srivastava N, Banerjee M (2013) Association of IL-6, TNF-Î± and IL-10 gene polymorphisms with type 2 diabetes mellitus. Mol Biol Rep 40: 6271-6279.
6. Kubaszek A, Pihlajamäki J, Komarovski V, Lindi V, Lindström J, et al. (2003) Promoter polymorphisms of the TNF-alpha (G-308A) and IL-6 (C-174G) genes predict the conversion from impaired glucose tolerance to type 2 diabetes: the Finnish Diabetes Prevention Study. Diabetes 52: 1872-1876.
7. Arababadi MK, Reza Mirzaei M, Ali Sajadi SM, Hassanshahi G, Ahmadabadi BN, et al. (2012) Interleukin (IL)-10 gene polymorphisms are associated with type 2 diabetes with and without nephropathy: a study of patients from the southeast region of Iran. Inflammation 35: 797-802.
8. Solaleh E, Arash H-n, Azam N, Mazaher R, Bagher L (2009) Promoter resistin gene polymorphism in patients with type 2 diabetes and its influence on concerned metabolic phenotypes. Journal of Diabetes and Metabolic Disorders 8: 150-156.
9. Motawi TM, Shaker OG, El-Sawalhi MM, Abdel-Nasser ZM (2014) Visfatin

-948G/T and resistin -420C/G polymorphisms in Egyptian type 2 diabetic patients with and without cardiovascular diseases. Genome 57: 259-266.

10. Patel L, Buckels AC, Kinghorn IJ, Murdock PR, Holbrook JD, et al. (2003) Resistin is expressed in human macrophages and directly regulated by PPAR gamma activators. Biochem Biophys Res Commun 300: 472-476.

11. Jung HS, Park KH, Cho YM, Chung SS, Cho HJ, et al. (2006) Resistin is secreted from macrophages in atheromas and promotes atherosclerosis. Cardiovasc Res 69: 76-85.

12. Sadashiv, Tiwari S, Paul BN, Kumar S, Chandra A, et al. (2012) Over expression of resistin in adipose tissue of the obese induces insulin resistance. World J Diabetes 3: 135-141.

13. Jiang CY, Wang W, Tang JX, Yuan ZR (2013) The adipocytokine resistin stimulates the production of proinflammatory cytokines TNF-Î± and IL-6 in pancreatic acinar cells via NF-ÎºB activation. J Endocrinol Invest 36: 986-992.

14. Silswal N, Singh AK, Aruna B, Mukhopadhyay S, Ghosh S, et al. (2005) Human resistin stimulates the pro-inflammatory cytokines TNF-alpha and IL-12 in macrophages by NF-kappaB-dependent pathway. Biochem Biophys Res Commun 334: 1092-1101.

15. Ikeda Y, Tsuchiya H, Hama S, Kajimoto K, Kogure K (2013) Resistin affects lipid metabolism during adipocyte maturation of 3T3-L1 cells. FEBS J 280: 5884-5895.

16. Wen F, Zhang H, Bao C, Yang M, Wang N, et al. (2015) Resistin Increases Ectopic Deposition of Lipids Through miR-696 in C2C12 Cells. Biochem Genet 53: 63-71.

17. Lee TS, Lin CY, Tsai JY, Wu YL, Su KH, et al. (2009) Resistin increases lipid accumulation by affecting class A scavenger receptor, CD36 and ATP-binding cassette transporter-A1 in macrophages. Life sciences 84: 97-104.

18. Palanivel R, Sweeney G (2005) Regulation of fatty acid uptake and metabolism in L6 skeletal muscle cells by resistin. FEBS Lett 579: 5049-5054.

19. Apalasamy YD, Rampal S, Salim A, Moy FM, Su TT, et al. (2015) Polymorphisms of the resistin gene and their association with obesity and resistin levels in Malaysian Malays. Biochem Genet 53: 120-131.

20. Ukkola O, Kunnari A, Kesäniemi YA (2008) Genetic variants at the resistin locus are associated with the plasma resistin concentration and cardiovascular risk factors. Regul Pept 149: 56-59.

21. Tsukahara T, Nakashima E, Watarai A, Hamada Y, Naruse K, et al. (2009) Polymorphism in resistin promoter region at -420 determines the serum resistin levels and may be a risk marker of stroke in Japanese type 2 diabetic patients. Diabetes Res Clin Pract 84: 179-186.

22. Tan MS, Chang SY, Chang DM, Tsai JC, Lee YJ (2003) Association of resistin gene 3'-untranslated region +62G-->A polymorphism with type 2 diabetes and hypertension in a Chinese population. J Clin Endocrinol Metab 88: 1258-1263.

23. Chen BH, Song Y, Ding EL, Manson JE, Roberts CK, et al. (2010) Association of resistin promoter polymorphisms with plasma resistin levels and type 2 diabetes in women and men. Int J Mol Epidemiol Genet 1: 167-174.

24. Chi S, Lan C, Zhang S, Liu H, Wang X, et al. (2009) Association of -394C>G and -420C>G polymorphisms in the RETN gene with T2DM and CHD and a new potential SNP might be exist in exon 3 of RETN gene in Chinese. Mol Cell Biochem 330: 31-38.

25. Boumaiza I, Omezzine A, Rejeb J, Rebhi L, Ben Rejeb N, et al. (2012) Association between four resistin polymorphisms, obesity, and metabolic syndrome parameters in Tunisian volunteers. Genet Test Mol Biomarkers 16: 1356-1362.

26. El-Shal AS, Pasha HF, Rashad NM (2013) Association of resistin gene polymorphisms with insulin resistance in Egyptian obese patients. Gene 515: 233-238.

27. Chavarria-Ávila E, Ruíz Quezada SL2, Guzmán-Ornelas MO3, Castro-Albarrán J4, Aguilar Aldrete ME5, et al. (2013) [Association of resistin gene 3'UTR+62G>A polymorphism with insulin resistance, adiposity and the adiponectin-resistin index in Mexican population]. Nutr Hosp 28: 1867-1876.

28. Nieva-Vazquez A, Pérez-Fuentes R, Torres-Rasgado E, López-López JG, Romero JR (2014) Serum resistin levels are associated with adiposity and insulin sensitivity in obese Hispanic subjects. Metab Syndr Relat Disord 12: 143-148.

29. Miller SA, Dykes DD, Polesky HF (1988) A simple salting out procedure for extracting DNA from human nucleated cells. Nucleic Acids Res 16: 1215.

30. Gustincich S, Manfioletti G, Del Sal G, Schneider C, Carninci P (1991) A fast method for high-quality genomic DNA extraction from whole human blood. Biotechniques 11: 298-300, 302.

31. DerSimonian R, Laird N (1986) Meta-analysis in clinical trials. Control Clin Trials 7: 177-188.

32. Miller JJ (1978) The Inverse of the Freeman – Tukey Double Arcsine Transformation. The American Statistician 32: 138-138.

33. Begg CB, Mazumdar M (1994) Operating characteristics of a rank correlation test for publication bias. Biometrics 50: 1088-1101.

34. Egger M, Smith GD, Schneider M, Minder C (1997) Bias in meta-analysis detected by a simple, graphical test. BMJ 315: 629-634.

35. Bouchard L, Weisnagel SJ, Engert JC, Hudson TJ, Bouchard C, et al. (2004) Human resistin gene polymorphism is associated with visceral obesity and fasting and oral glucose stimulated C-peptide in the Québec Family Study. J Endocrinol Invest 27: 1003-1009.

36. Cauchi S, Nead KT, Choquet H, Horber F, Potoczna N, et al. (2008) The genetic susceptibility to type 2 diabetes may be modulated by obesity status: implications for association studies. BMC Med Genet 9: 45.

37. Cho YM, Youn BS, Chung SS, Kim KW, Lee HK, et al. (2004) Common genetic polymorphisms in the promoter of resistin gene are major determinants of plasma resistin concentrations in humans. Diabetologia 47: 559-565.

38. Engert JC, Vohl MC, Williams SM, Lepage P, Loredo-Osti JC, et al. (2002) 5' flanking variants of resistin are associated with obesity. Diabetes 51: 1629-1634.

39. Hishida A, Wakai K, Okada R, Morita E, Hamajima N, et al. (2013) Significant interaction between RETN -420 G/G genotype and lower BMI on decreased risk of type 2 diabetes mellitus (T2DM) in Japanese--the J-MICC Study. Endocrine journal 60: 237-243.

40. Kunnari A, Ukkola O, Kesaniemi YA (2005) Resistin polymorphisms are associated with cerebrovascular disease in Finnish Type 2 diabetic patients. Diabetic medicine : a journal of the British Diabetic Association 22: 583-589.

41. Lau CH, Muniandy S (2011) Adiponectin and resistin gene polymorphisms in association with their respective adipokine levels. Ann Hum Genet 75: 370-382.

42. Ma X, Warram JH, Trischitta V, Doria A (2002) Genetic variants at the resistin locus and risk of type 2 diabetes in Caucasians. J Clin Endocrinol Metab 87: 4407-4410.

43. Ochi M, Osawa H, Hirota Y, Hara K, Tabara Y, et al. (2007) Frequency of the G/G genotype of resistin single nucleotide polymorphism at -420 appears to be increased in younger-onset type 2 diabetes. Diabetes 56: 2834-2838.

44. Beckers S, Peeters AV, Freitas Fd, Mertens IL, Hendrickx JJ, et al. (2008) Analysis of genetic variations in the resistin gene shows no associations with obesity in women. Obesity (Silver Spring) 16: 905-907.

45. Gouni-Berthold I, Giannakidou E, Faust M, Kratzsch J, Berthold HK, et al. (2005) Resistin gene 3'-untranslated region +62G-->A polymorphism is associated with hypertension but not diabetes mellitus type 2 in a German population. J Intern Med 258: 518-526.

46. Jiang B, Liu Y, Liu Y, Fang F, Wang X, et al. (2014) Association of four insulin resistance genes with type 2 diabetes mellitus and hypertension in the Chinese Han population. Mol Biol Rep 41: 925-933.

47. Huang T, Qi Q, Zheng Y, Ley SH, Manson JE, et al. (2015) Genetic Predisposition to Central Obesity and Risk of Type 2 Diabetes: Two Independent Cohort Studies. Diabetes Care 38: 1306-1311.

48. Emanuela F, Grazia M, Marco de R, Maria Paola L, Giorgio F, et al. (2012) Inflammation as a Link between Obesity and Metabolic Syndrome. J Nutr Metab 2012: 476380.

49. Gregor MF, Hotamisligil GS (2011) Inflammatory mechanisms in obesity. Annu Rev Immunol 29: 415-445.

50. Spranger J, Kroke A, Möhlig M, Hoffmann K, Bergmann MM, et al. (2003) Inflammatory cytokines and the risk to develop type 2 diabetes: results of the prospective population-based European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam Study. Diabetes 52: 812-817.

51. King GL (2008) The role of inflammatory cytokines in diabetes and its complications. J Periodontol 79: 1527-1534.

52. Moreno-Estrada A, Gignoux CR, Fernández-López JC, Zakharia F, Sikora M,

et al. (2014) Human genetics. The genetics of Mexico recapitulates Native American substructure and affects biomedical traits. Science 344: 1280-1285.

53. Wen Y, Lu P, Dai L (2013) Association between resistin gene -420 C/G polymorphism and the risk of type 2 diabetes mellitus: a meta-analysis. Acta Diabetol 50: 267-272.

54. Yu Z, Han S, Cao X, Zhu C, Wang X, et al. (2012) Genetic polymorphisms in adipokine genes and the risk of obesity: a systematic review and meta-analysis. Obesity (Silver Spring) 20: 396-406.

55. Smith SR, Bai F, Charbonneau C, Janderová L, Argyropoulos G (2003) A promoter genotype and oxidative stress potentially link resistin to human insulin resistance. Diabetes 52: 1611-1618.

56. Mattevi VS, Zembrzuski VM, Hutz MH (2004) A resistin gene polymorphism is associated with body mass index in women. Hum Genet 115: 208-212.

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