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Association of Taq 1B *CETP* polymorphism with insulin and HOMA levels in the population of the Canary Islands

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HOMA

Abstract *Background and aims:* Cholesteryl ester transfer protein (CETP) is an enzyme with a key role in lipoprotein metabolism. A common genetic polymorphism, the Taq 1B, influences CETP activity and HDL-cholesterol levels, with individual homozygotes for the B1 allele exhibiting higher enzyme activity and lower HDL-cholesterol levels than carriers of at least one B2 allele. Our aim was to analyze the influence of Taq 1B *CETP* polymorphism on cardiovascular risk factors in a representative sample of adult subjects from Canary population.
Methods and result: A total of 518 adult subjects from the Canary Islands, enrolled in a nutritional survey (the ENCA study), were included. The Taq 1B polymorphism was analyzed by PCR—RFLP. Compared with individuals with at least one B2 allele, and after adjusting for age, sex, BMI, waist perimeter, smoking and alcohol intake, carriers of the B1B1 genotype showed lower HDL-cholesterol levels (geometric mean (95% CI): 46.6 (44.5—48.8) vs. 50.6 (49.1—52.9) mg/dl; $P = 0.003$); and higher insulin (geometric mean (95% CI): 11.1 (10.5—11.9) vs. 10.0 (9.5—10.5 μU/ml; $P = 0.008$) and HOMA levels (geometric mean (95% CI): 2.3 (2.1—2.5) vs. 2.1 (1.9—2.1); $P = 0.009$). In addition, the B1B1 genotype was more frequent in individuals who had low levels of HDL-cholesterol according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) criteria (Odds Ratio (OR): 1.563; 95% CI: 1.04—2.34; $P = 0.030$), and in those included in the upper quartile of insulinemia (OR: 1.90; 95% CI: 1.20—3.03; $P = 0.007$) and HOMA (OR: 1.61; 95% CI: 1.02—2.57; $P = 0.043$).

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Conclusion: The observed influence of Taq 1B polymorphism on insulin levels and HOMA highlights the possible role of CETP in the regulation of glucose homeostasis.
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Introduction

Cholesteryl ester transfer protein (CETP) is a hydrophobic glycoprotein secreted mainly by the liver and to a lesser extent by adipose tissue and the spleen. It circulates in the plasma associated with high-density lipoprotein (HDL) particles [1,2]. CETP mediates the transference of esterified cholesterol from HDL to apolipoprotein B-containing lipoproteins, and of triglycerides, mainly from very low-density lipoproteins, to low-density lipoproteins (LDL) and HDL. This process gives rise to an enrichment of triglycerides of HDL and LDL, which become good substrates for hepatic lipase and lipoprotein lipase. The net result is a decrease of plasma levels of HDL-cholesterol (HDL-C) and an increase in the levels of small dense LDL particles [3]. Thus, CETP plays an important role in the reverse cholesterol transport, since it promotes the return of esterified cholesterol to the liver through the LDL-receptor [1,4]. In fact, mutations in the *CETP* gene, which cause a decrease in its expression or a truncated non-functional protein, cause an increase in plasma levels of HDL-C with slight decreases in plasma levels of LDL-C [5—7].

Diverse polymorphisms have been described in the *CETP* gene. The most studied is the Taq 1B (rs708272). It is located in the intron 1 of the *CETP* gene and consists of the substitution of a guanine by cytosine [8], giving rise to the B1 and B2 alleles, respectively. The B1 allele has a frequency of about 60% in Asiatic populations [9,10] and slightly higher in Europeans [11,12]. It is associated with higher CETP activity and thus lower levels of HDL-C than the B2 allele [13,14]. In multivariate analysis, this polymorphism accounts for about a 5% variation in HDL-C levels, after adjusting for diverse covariates [11,15,16]. In addition, the Framingham Study showed that carriers of the B1 allele have an increased risk of developing cardiovascular disease [14,17].

The Taq 1B polymorphism has been mainly studied regarding its relationship with HDL-C levels and the risk of cardiovascular disease. Recent studies also suggest that CETP polymorphism could have influence on the development of the metabolic syndrome, as carriers of the B2 allele having a reduced risk [18], which point toward a protective role of the B2 allele on the development of insulin resistance. Thus, the aim of the present study was to evaluate the effect of polymorphism of lipid metabolic variables and its relationship with parameters of insulin resistance in a series of individuals who are representatives of the population of the Canary Islands (Spain).

Methods

Study population

The Canary Islands are located in the Atlantic Ocean, near to the North African coast. They have belonged to Spain since the XV century, and the population is primarily of Spanish origin. In the Canarian Nutrition Survey (ENCA 1997—1998) [19] a representative sample of the Canarian general population between 6-year-old and 75-year-old was selected by a two-stage stratified sampling method. Details on the methodology have been published elsewhere [19].

ENCA included two individual questionnaires about diet, lifestyle and health status. Anthropometric variables and blood pressure were also measured. Participants in these home surveys were solicited to have a blood extraction in order to determine biochemical parameters. Seven hundred and eighty-two subjects participated in the biochemical phase (44.8% of the ENCA participants). The present study is based on a sub-sample of 518 adult (234 men and 284 women) who met the following inclusion criteria: (a) available samples for genetic analyses; (b) complete data on physical and laboratory measurements; and (c) age between 18 and 69 years. Body mass index (BMI) was calculated as weight (in kg) divided by height (in m^2). Individuals were considered diabetic if they either self-reported a previous diagnosis of diabetes or had a fasting serum glucose level $\geq$ 126 mg/dl [20]. Thirty-nine individuals (7.5%) met the criteria for diabetes. These individuals were excluded from analysis involving variables related to glucose homeostasis, such as insulin, glucose and HOMA.

The study was approved by the Institutional Committee of Ethics of the Canarian Health Service, and all the study participants gave written informed consent.

Laboratory measurements

Blood samples were obtained after a 12—14-h fast for the determination of biochemical and genetic parameters. Serum total cholesterol, triglyceride (TG), high-density lipoprotein cholesterol (HDL-C) and glucose levels were measured by standard protocols. Low-density lipoprotein cholesterol (LDL-C) was calculated with Friedewald formula [21,22]. Insulin was measured with a solid-phase radioimmunoassay (Diagnostic Products Corporation, Los Angeles, CA). Insulin resistance was estimated with the Homeostasis Model Assessment (HOMA), employing fasting serum insulin and glucose concentrations [23]. The formula for the model follows:

$$[\text{HOMA} = \text{Fasting insulin } (\mu\text{U/ml}) \times \text{fasting glucose } (\text{mmol/l})/22.5]$$

Genetic analysis

Genomic DNA from blood samples was isolated using a DNA Isolation Kit (Puregene, Gentra Systems, Minneapolis, USA). A fragment of 1000 bp in intron 1 of the *CETP* gene was amplified by polymerase chain reaction (PCR) using allele-specific oligonucleotides: 5′-AAG GCC TGC TCC AAA GGC

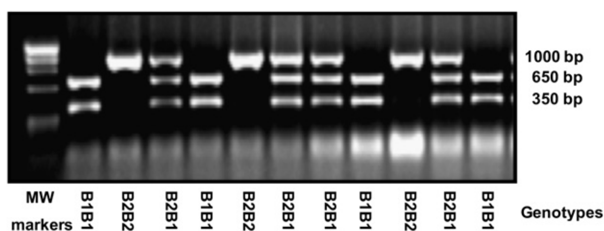

Figure 1 PCR—RFLP agarose gel. The figure shows the DNA bands after digestion with Taq 1B enzyme. The 1000 bp band represents the amplified DNA fragment without the restriction site and corresponds to the B2 allele; the 650 and 350 bp bands come from the original 1000 bp band that included the restriction site for Taq 1B and correspond to the B1 allele.

ACC TCG CAC-3′ (sense) and 5′-CTG GAT CAC CTT GGC AGT CTC GTG G-3′ (antisense) according to the methods described by Wu et al. [9]. The PCR products were then digested in presence of the Taq 1B restriction enzyme. The restriction fragments of 1000, 650 and 350 bp were analyzed on agarose gels (Fig. 1).

Statistical analyses

Data are presented as the mean ± standard deviation (SD). Variables that were not normally distributed, as judged by the Kolmogorov—Smirnov test, were logarithmically transformed to improve the skewness and kurtosis of their distribution for statistical testing. The allele frequency of the *CETP* polymorphism was estimated by gene counting. The cases observed for each *CETP* genotype were compared with those predicted by the Hardy—Weinberg equilibrium using the Chi-square test.

Univariate comparisons of variables among the genotypes were done using the Student's *t*-test, whereas proportions were compared using the Chi-square statistical test with Yates' correction. Multivariate analyses of HDL-C, insulin and HOMA were developed in relation to *CETP* genotypes, adjusting for diverse confounders, and included analysis of covariance (ANCOVA) for continuous variables and logistic regression analysis for dichotomous variables. Significant differences were assumed if a two tailed $P < 0.05$ was achieved. These analyses were performed with the SPSS V.13 statistical package (SPSS, Chicago, IL, USA). Comparison of the regression lines, with respect to slopes and intercepts, in the correlation between BMI and insulin and HOMA levels, was conducted by ANCOVA using the GraphPad Prism version 4.00 for Windows (GraphPad Software, San Diego, California, USA).

Results

Genotype frequency of the Taq 1B polymorphism in the whole series was as follows: 16.4% for B2B2 ($n = 85$), 45.9% for B2B1 ($n = 238$), and 37.6% for B1B1 ($n = 195$). Allele frequencies were 39.4% and 60.6% for the B2 and B1 alleles, respectively. Genotype frequency was not significantly different from that predicted by the Hardy—Weinberg equilibrium (data not shown). Given the low number of individuals carrying the B2B2 genotype ($n = 85$), they were grouped with individuals with the B2B1 genotype ($n = 238$), thus forming a group comprising 323 individuals carrying at least a B2 allele. This group was designated as having the ''non-B1B1 genotype'' in figures and tables.

Anthropometric, demographic and metabolic characteristics of the entire cohort, and individuals grouped according to their Taq 1B genotypes are shown in Table 1. There were no differences in the age, BMI, waist circumference, or serum levels of LDL-C, triglycerides, and glucose across the Taq 1B genotypes. However, carriers of the B1B1 genotype had significantly lower levels of HDL-C compared with those carrying at least one B2 allele

Table 1 Anthropometric, demographic and metabolic characteristics of the entire cohort and individuals grouped by genotype.

Variable	Whole series ($n = 518$)	Taq 1B genotypes		P
		Non-B1B1 ($m = 323$)	B1B1 ($m = 195$	
Age (years)	46.1 ± 15.4	46.4 ± 15.1	45.6 ± 15.9	ns
Sex (male/female)	234/284	147/176	87/108	ns
BMI (kg/m^2)	26.7 ± 5.3	26.6 ± 5.0	26.8 ± 5.7	ns
Waist (cm)	89.8 ± 13.7	89.7 ± 13.6	90.0 ± 14.0	ns
Cholesterol (mmol/l)	5.60 ± 1.34	5.64 ± 1.40	5.53 ± 1.23	ns
HDL-C (mmol/l)	1.36 ± 0.45	1.40 ± 0.46	1.29 ± 0.44	0.006
LDL-C (mmol/l)	3.59 ± 1.25	3.60 ± 1.29	3.58 ± 1.60	ns
Triglyceride (mmol/l)	1.41 ± 0.83	1.40 ± 0.87	1.42 ± 0.76	ns
Glucose* (mg/dl)	4.63 ± 0.76	4.60 ± 0.76	4.66 ± 0.77	ns
Insulin* (μU/ml)	11.8 ± 6.4	11.1 ± 5.3	12.9 ± 7.8	0.004
HOMA*	2.5 ± 1.6	2.3 ± 1.3	2.7 ± 1.9	0.006

S.D.: standard deviation.
ns = non significant.
* Individuals considered diabetic were excluded ($n = 39$). The P value was computed with the Chi-square test (in the case of proportions of males and females throughout genotypes) and the Student's t-test for the remaining variables.

Table 2 Analysis of covariance of the influence of Taq 1B polymorphism on the levels of HDL-C, insulin and HOMA.

Variables	Genotype	Geometric mean (95% CI)	*P*
HDL-C (mmol/l)	Non-B1B1	1.31 (1.27—1.37)	0.003
	B1B1	1.20 (1.15—1.26)	
Insulin (μU/ml)	Non-B1B1	10.0 (9.5—10.5)	0.008
	B1B1	11.1 (10.5—11.9)	
HOMA	Non-B1B1	2.1 (1.9—2.1)	0.009
	B1B1	2.3 (2.1—2.5)	

Adjustments were made for age, sex, BMI, waist circumference, smoking and alcohol drinking. Insulin and HOMA levels were analyzed in individuals considered nondiabetic ($n = 479$); 95% CI: 95% confidence interval.

(50.0 ± 17.0 mg/dl vs. 54.1 ± 17.9 mg/dl; $P = 0.006$). Interestingly, carriers of the B1B1 genotype had higher values of fasting insulin and HOMA compared with individuals carrying at least one B2 allele (12.9 ± 7.8 μU/ml vs. 11.1 ± 5.3 μU/ml, $P = 0.006$; and 2.7 ± 1.9 vs. 2.3 ± 1.3 $P = 0.006$). This influence remained significant after adjusting for age, sex, BMI, waist circumference, current tobacco use and alcohol consumption (Table 2).

Given the well-known influence of adiposity on fasting values of insulin and HOMA, it was of interest to study the impact of the polymorphism on the correlation between BMI and fasting levels of insulin and HOMA. Results are depicted in Fig. 2 and the regression analysis is shown in Table 3. The slopes of the regression lines did not differ significantly between genotypes; in fact, the regression lines were almost parallel. However, the *Y*-intercept of the line representing individuals with the B1B1 genotype was significantly higher for both insulin and HOMA, which suggests that for any given value of BMI, individuals with the B1B1 genotype exhibit higher values of insulin and HOMA compared with those carrying at least one B2 allele.

Table 4 shows the changes in genotype frequencies when values of HDL-C were dichotomized as ''low'' or ''normal'' according to the criteria of the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) [24], and the International Diabetes Federation criteria (HDL-C lower than 50 mg/dl for women and 40 mg/dl for men). In addition, values of insulin and HOMA were considered ''high'' or ''normal'' according to the 75th percentile, in agreement with the diagnostic criteria for insulin resistance proposed by the European Group for the Study of Insulin Resistance (EGIR) [25] The frequency of the B1B1 genotype was significantly increased in individuals within the upper quartile of insulinemia and HOMA, and those considered to have a low level of HDL-C. These results were confirmed by a binary logistic regression analysis (also showed in Table 4), after adjusting for several confounding variables such as age, sex, BMI, waist circumference, smoking and alcohol drinking. The B1B1 genotype conferred a greater risk of having low levels of HDL-C (OR = 1.563; 95% CI: 1.044—2.341; $P = 0.030$) and high levels of fasting serum insulin (OR = 1.904; 95% CI: 1.197—3.029; $P = 0.007$) and HOMA (OR = 1.614; 95% CI: 1.016—2.565; $P = 0.043$).

Discussion

Two main findings can be highlighted from the results presented above: (1) the CETP polymorphism influences HDL-C levels, with individuals carrying the B1B1 genotype showing lower levels than those carrying at least one B2 allele, and (2) the CETP polymorphism can modulate the insulin sensitivity.

There are many studies showing an inverse relationship between CETP activity and HDL-C levels, which may explain the role that CETP plays in the development of cardiovascular disease [11,17,26]. From our results, it seems clear that the polymorphism can influence serum levels of HDL-C, with individual homozygotes for the B1 allele having lower levels than carriers of at least one B2 allele. This finding is in agreement with previous reports, and can be explained by the intrinsic activity of CETP, which is greater in individuals carrying the B1B1 genotype [13]. On the other hand, we have found that insulin and HOMA levels are increased in carriers of the B1B1 genotype, suggesting the influence of polymorphism on both parameters of insulin resistance.

The relationship between insulin and CETP activity remains controversial. Diverse authors have found that CETP activity is increased in obese and diabetic subjects [27—29]. It has been postulated that insulin resistance,

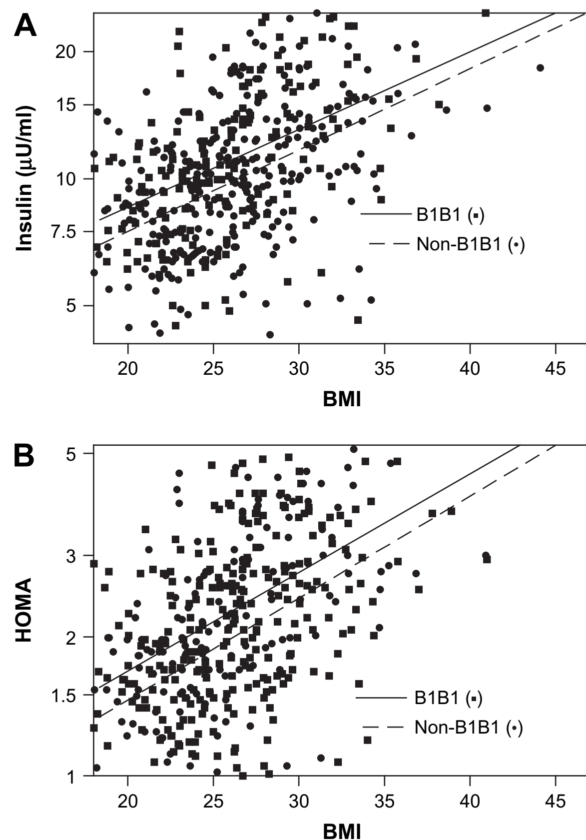

Figure 2 Effect of Taq 1B polymorphism on the correlation between insulin (A) and HOMA (B) with BMI.

Table 3 Analysis of the correlation between BMI and insulin and HOMA levels for each Taq 1B genotype depicted in Fig. 1.

Variable	Genotype	*n*	*r*	*P*	Slope	*P*	*Y*-intercept ($X = 0$)	*P*	Estimated values of insulin (μU/ml) and HOMA		
									BMI = 20	BMI = 25	BMI = 30
Insulin	Non-B1B1	300	0.484	<0.001	0.0445		3.10		7.51	9.38	11.73
	B1B1	179	0.475	<0.001	0.0425	NS	3.67	0.002	8.58	10.60	13.12
HOMA	Non-B1B1	300	0.471	<0.001	0.0509		0.527		1.46	1.88	2.43
	B1B1	179	0.481	<0.001	0.0551	NS	0.631	0.002	1.69	2.16	2.86

Individuals considered diabetic ($n = 39$) were excluded from the analysis. NS: not significant; *r*: Pearson's correlation coefficient. Values of insulinemia and HOMA for a given BMI values equal to 0 (*Y*-intercept), 20, 25 and 30 were deduced from the regression lines and are presented as antilogarithms.

secondary to obesity, is responsible for this alteration [30–32]. Insulin could have a suppressor effect on the mRNA transcription of *CETP*, which could explain its increase in the presence of insulin resistance. However, this effect could be indirect, since the high levels of triglycerides (a frequent finding in insulin resistance) have also been proposed to mediate this effect [33,34]. Since individuals homozygotes for the B1 allele have an increased CETP activity, they should have an increased triglyceride content in their HDL particles, which in turn would became a good substrate for the hepatic lipase. Thus, individuals with the B1B1 genotype would have an increased flux of free fatty acids to the liver from HDL that would decrease the hepatic sensitivity to insulin, which would explain the results presented here. Evidently, more studies are needed in order to confirm or reject this hypothesis.

Despite the fact that diverse studies have focused on the relationship between CETP and parameters of insulin resistance and a recent paper had concluded that the B2 allele reduces the risk of the metabolic syndrome [18], none of them analyzed the contribution of the Taq 1B genotype to insulin and HOMA levels. Thus, the present results could add new insight into the role of CETP on glucose homeostasis.

In our series, 16 (41%) of the 39 individuals considered as diabetic belonged to the B1B1 genotype. Within nondiabetic individuals ($n = 479$), 179 of them (37%) carried the B1B1 genotype. These differences, although nonsignificant, would point to a protective role of the B2 allele on the development of diabetes mellitus. Obviously a deeper analysis involving individuals with different abnormalities of glucose homeostasis, i.e., impaired fasting glucose, impaired glucose tolerance, type-2 diabetes and healthy individuals would help to determine the exact influence of the polymorphism on the risk of developing type-2 diabetes mellitus.

Conflict of interest

All authors declare that no conflict of interest exists that could be perceived as prejudicing the impartiality of the research.

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Table 4 Changes in genotype frequency throughout HDL-C insulin and HOMA categories.

Variable		Genotype		OR (95% CI)*	*P*	OR (95% CI)**	*P*
		Non-B1B1	B1B1				
HDL-C (F/M)[a]	≥50/40 mg/dl	69.3% (224)	59.0% (115)	1		1	
	<50/40 mg/dl	30.7% (99)	41.0% (80)	1.57 (1.09–2.28)	0.016	1.56 (1.04–2.34)	0.030
Insulin-75[b]	<13.75 μU/ml	78.7% (236)	68.7% (123)	1		1	
	≥13.75 μU/ml	21.3% (64)	31.3% (56)	1.68 (1.10–2.56)	0.015	1.90 (1.20–3.03)	0.007
HOMA-75[b]	<2.923	78.0% (234)	69.8% (125	1		1	
	≥2.923	22.0% (66)	30.2% (54)	1.53 (1.01–2.33)	0.046	1.61 (1.02–2.57)	0.043

Numbers in parentheses show the number of individuals.
[a] According to the NCEP-ATPIII and IDF guidelines for HDL-cholesterol (F: female; M: male).
[b] According to WHO and EGIR criteria for insulin resistance. OR: odds ratio; 95% CI: 95% confidence interval, either without adjustments (*) or after adjustment (**) for age, sex, BMI, waist circumference, smoking habit and alcohol consumption.

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