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ORIGINAL ARTICLE

R230C but not − 565C/T variant of the *ABCA1* gene is associated with type 2 diabetes in Mexicans through an effect on lowering HDL-cholesterol levels

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Abstract

Purpose Type 2 diabetes (T2D) and low serum concentration of high-density lipoprotein cholesterol (HDL-c) are common coexisting metabolic disorders. *ABCA1* variants have been shown to be associated to these conditions. We sought to test the combined effect of two *ABCA1* gene common variants, rs2422493 (− 565C > T) and rs9282541 (R230C) on HDL-c levels and T2D risk.

Methods Path analysis was conducted in 3,303 Mexican-mestizos to assess the specific contributions of rs2422493 and rs9282541 *ABCA1* variants, insulin resistance, waist-to-height ratio (WHtR), and age on HDL-c levels and T2D risk. Participants were classified into four groups according to their *ABCA1* variants carrier status: (i) the reference group carried wild type alleles for both *ABCA1* variants (−/−), (ii) +/− were carriers of rs2422493 but non-carriers of rs9282541, (iii) −/+ for carriers of rs9282541 but not carriers of rs2422493 and (iv) carriers of minor alleles for both SNPs (+/+). Principal components from two previous genome-wide association studies were used to control for ethnicity.

Results We identified significant indirect effects on T2D risk mediated by HDL-c in groups −/+ and +/+ ($\beta = 0.04$; $p = 0.03$ and $\beta = 0.06$; $p < 0.01$, respectively) in comparison to the −/− reference group. Low concentrations of HDL-c were directly and significantly associated with increased T2D risk ($\beta = -0.70$; $p < 0.01$). WHtR, male gender, age, and insulin resistance were also associated with T2D risk ($p < 0.05$). There was no significant direct effect for any of the *ABCA1* groups on T2D risk: $p = 0.99$, $p = 0.58$, and $p = 0.91$ for groups +/−, −/+, and +/+ respectively.

Conclusions The *ABCA1* rs9282541 (R230C) allele is associated with T2D in Mexicans through its effect on lowering HDL-c levels. This is the first report demonstrating that HDL-c levels act as an intermediate factor between an *ABCA1* variant and T2D.

Keywords *ABCA1* · HDL · HDL-c · Hypoalphalipoproteinemia · Type 2 diabetes · rs2422493 · rs9282541

Introduction

Type 2 diabetes (T2D) and low serum concentration of high-density lipoprotein cholesterol (HDL-c, i.e., hypoalphalipoproteinemia) are very prevalent metabolic conditions associated with high morbidity and mortality in the Mexican population [1, 2]. Both disorders are strongly influenced by lifestyle [3, 4] and genetic factors [5, 6]. Of particular interest is the recognition of genetic variants derived from Amerindian ancestry that have a large effect on various metabolic traits, including dyslipidemias such as hypertriglyceridemia [7, 8], hypoalphalipoproteinemia (HA) [9-11], obesity [12], and T2D [13]. Among such variants, the *ABCA1* polymorphism rs9282541 (R230C), which is almost exclusively present in Amerindian and Amerindian-derived populations, has been associated with low HDL-c levels [9, 10, 14, 15], T2D [13] and obesity [15]. On the other hand, the C to T polymorphism at position − 565 (rs2422493) in the *ABCA1*

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gene promoter results in decreased transactivation activity of a reporter gene in vitro and presumably lowers the expression of *ABCA1* in vivo [16]. In addition, cell lines expressing the *ABCA1* C230 allele (rs9282541) exhibit a cholesterol efflux that is 27% lower than what is observed in cells expressing the wild-type R230 allele [14]. These two *ABCA1* polymorphisms are frequent in Mexicans; rs2422493 and rs9282541 having minor allele frequencies of 0.5 and 0.11 [10], respectively.

The ATP-binding cassette transporter A1 (ABCA1) participates in the initial synthesis of HDL molecules mainly in the liver through binding to the lipid-free apolipoprotein A1 [17-19], but it also transfers cholesterol from peripheral cells to lipid-poor apoAI [20, 21]. In animal models, it has been shown that impaired *ABCA1* function leads to β-cell dysfunction through decreasing cholesterol efflux [22] and contributing to decreased insulin secretion. Epidemiological evidence suggests that low HDL-c levels [23-25], as well as low HDL-c/apoAI and HDL-c/apoAII ratios are independent risk factors for incident T2D (25). Moreover, it has been previously recognized that HDL and apoAI molecules promote insulin synthesis and insulin secretion in pancreatic β-cells [26], MIN-6 cells, and rat islet cells [27].

The objective of this study was to elucidate the combined effect of two common *ABCA1* variants on HDL-c levels and T2D risk. Therefore, through a path analysis we tested the direct and indirect effects of two common *ABCA1* gene variants, rs2422493 and rs9282541, on HDL-c levels and T2D risk in a cohort of 3,303 Mexicans.

Patients and methods

Study group

Mexican-mestizo individuals (with parents and grandparents born in Mexico) who were 18 years and older and who had participated in at least one of two previous GWAS for triglycerides (GWAS-TG) [7] or T2D (GWAS-T2D) [28] were included. Briefly, most of the participants were recruited at the outpatient diabetes clinic of the Department of Endocrinology and Metabolism of the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán (INCMNSZ) in Mexico City. In addition, a cohort of normoglycemic government employees aged 45 years or older constituted the control group. The resulting study cohort consisted of 914 T2D cases and 2,389 control individuals. T2D was diagnosed based on American Diabetes Association criteria [29]. The Committee of Ethics and the Institutional Review Board of the INCMNSZ on human subjects research approved the study protocol. This study conforms to the ethical guidelines of the 1975 Declaration of Helsinki [30]. All individuals provided written informed consent.

Clinical and laboratory analyses

BMI was calculated as weight (in kg) divided by height (in m^2), and waist-to-height ratio (WHtR) was assessed dividing waist size by height, both measured in cm. We included the WHtR because it is a better index than BMI and waist circumference (WC) for detecting cardiometabolic risk factors linked to central obesity [31, 32]. Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) was calculated according to the formula: fasting insulin (microU/L)*fasting glucose (nmol/L)/22.5. Trained personnel measured the weight, height, and waist circumference of all participants. The diagnosis of HA was considered when women had HDL-c < 1.3 mmol/L, and men < 1.04 mmol/L. For biochemical analyses, blood samples were obtained after a 9- to 12-h fast. Blood glucose concentration was measured by using the glucose oxidase method, and total cholesterol, HDL-c, and triglycerides concentrations were measured using a Synchron Autoanalyzer (Beckman Co). LDL-c was estimated from total cholesterol as described by Friedewald et al. [33]. Genomic DNA was extracted from total blood samples using a QIAamp 96 DNA Blood kit, Qiagen. Both *ABCA1* rs2422493 and rs9282541 variants were genotyped using Taqman probes. In addition, since all individuals had participated in at least one GWAS, the respective principal components (PCs) were available for estimating ethnicity.

Statistical analysis

Participants were grouped according to their carrier status on *ABCA1* variants in such way that four groups were formed. The reference group consisted of individuals having wild type alleles for both *ABCA1* variants (herein denoted as −/−). The "+" sign is being used for carriers of either one or two of the risk alleles as follows: The +/– group corresponds to individuals are either heterozygous or homozygous for the rs2422493 variant but non-carriers of rs92822541. Group −/+ includes individuals carrying rs92822541 in heterozygous or homozygous state, but without risk alleles for rs2422493 variant; and finally, the +/+ group refers to individuals carrying both rs2422493 and rs9282541 variants in either heterozygous or homozygous state.

Demographic and clinical characteristics were described and compared between groups. Differences were assessed using Mann–Whitney *U* test (for non-parametric quantitative distributions in two groups) or Kruskal–Wallis (for non-parametric quantitative variables distributed in more than two groups) and chi-squared test (for differences between proportions). Finally,

Dunn–Bonferroni post hoc method was used to correct for multiple comparison testing. Genotype frequencies of both variants were evaluated. Hardy–Weinberg equilibrium was determined in healthy controls using chi-squared tests. Linkage disequilibrium (LD) was assessed using r^2 statistic.

Because PCs from previous GWAS (GWAS-TG [7] and GWAS-T2D [28]) were available and the Native-American ancestry percentage of 484 individuals was also known (previously obtained by global ancestry calculation), the correlation between the first PC of GWAS-T2D and the percent of Native American ethnicity was computed. The correlation between the first PC of GWAS-TG and the first PC of GWAS-T2D was calculated and determined to be highly correlated. Thus, through a simple linear regression model, the values of the PC from GWAS-T2D were imputed for those who only had PC from GWAS-TG. As a result, a single index of ethnicity was obtained and used for adjusting for population stratification.

To assess the direct and indirect effects between *ABCA1* variants and HDL-c and T2D, path analysis was used. Because the mediating variable was not sampled under the case–control design, we performed the prevalence-weighted approach suggested by VanderWeele and Vansteelandt [34] aiming to avoid potential bias estimation. Path analysis is a multivariate statistical method consisting of simultaneous regression equations where continuous or categorical outcomes may be included. This method has been applied in the Framingham study to assess the role of genetic variants on metabolic diseases [35, 36]. Gender, age, ethnicity, and the *ABCA1* groups were the independent variables. HDL-c, WHtR, HOMA-IR and T2D were the dependent variables. A theoretical path model was specified based on prior findings of *ABCA1* variant R230C associated to T2D [13]; and of previously reported association between the C230 allele of the rs9282541 with BMI [14, 15], and insulin resistance with low expression of ABCA1 in visceral adipose tissue in humans [37]. Because T2D is a dichotomous endogenous variable, Theta parameterization was used and bias corrected standard errors were obtained through the Bootstrap approach. To increase parsimony, non-significant paths were removed. In all cases, and regardless of the p value, the assessment of the genetic effects on T2D, HDL-c, WHtR and HOMA-IR were always adjusted for ethnicity. Furthermore, the direct effects were always taken into account for assessing indirect effects. Goodness-of-fit of the final model was assessed using indices such as the standardized summary of the average covariance residuals [root mean square error of approximation (RMSEA)], Comparative fit index (CFI) and Tucker-Lewis index (TLI). We used Mplus v.8.3 software [38].

Results

Genotype frequencies for both SNPs were in Hardy–Weinberg equilibrium ($p > 0.05$). Genotype frequencies of the − 565C > T (rs2422493) SNP in all study subjects were as follows: CC 0.268 (886/3303), CT 0.495 (1636/3303) and TT 0.237 (781/3303). Allele frequencies were 0.52 for the C-allele and 0.48 for the T-allele. Regarding the genotype frequencies of the R230C (rs9282541) variant were CC 0.797 (2632/3303), CT 0.19 (627/3303), and TT 0.013 (44/3303). Allele frequencies were 0.88 for the C-allele and 0.12 for the T-allele. Both variants were in Hardy–Weinberg equilibrium ($p = 0.66$ and $p = 0.41$, respectively). Importantly, these two *ABCA1* variants (rs2422493 and rs9282541) are inherited as independent linkage disequilibrium blocks $r^2 = -0.1$.

The description of the main anthropometric and biochemical measurements across the four *ABCA1* groups are shown in Table 1. Largely, gender and age showed significant differences among groups ($p = 0.04$ and $p = 0.05$ respectively). The group −/+ had a predominance of males, while individuals in the group −/− were older than group +/+. Moreover, HA was significantly higher between +/+ vs. +/− and −/− (71.2% vs. 58.5%, $p < 0.001$, in both cases); thus, carriers of rs9282541 variant have a higher HA frequency than non-carriers.

When we compared anthropometric and biochemical characteristics according to the number of rs2422493 risk alleles (0, 1 or 2 risk alleles), we did not find any clinical or laboratory differences (data not shown). In contrast, for the three genotype combinations of rs9282541 (CC, CT and TT) we observed that, according to the nominal p value, HDL-c plasma levels were higher among subjects with the CC genotype compared to those with the CT ($p < 0.001$) or TT genotype ($p < 0.001$); interestingly, concentrations of HDL-c were slightly lower in individuals with two risk alleles (TT) in comparison to those carrying only one T allele ($p = 0.037$). Also, CT carriers were younger than CC ($p = 0.002$) or TT carriers ($p = 0.017$) (Supplementary table).

Population stratification correction

We built a single ethnicity index based on our findings of a correlation of 0.83 between the first PC of GWAS-T2D and the GWAS-TG, and of 0.91 between the first PC of GWAS-T2D and percent of Native-American ethnicity was 0.91. Thus, the use of the first PC of GWAS-T2D would adequately discriminate between American and European ethnicity. We included this index in our analyses to control for potential confounding due population stratification.

Table 1 Clinical and biochemical parameters of the study participants by *ABCA1* genotypes

Characteristics	−/− (667)	+/− (1965)	−/+ (219)	+/+ (452)	*p* value
Male gender, *n* (%)	274 (41.1)	823 (41.9)	113 (51.6)	186 (41.2)	0.036
Age, median (IQR), years	49 (42–58)	49 (42–57)	48 (40–55)	48 (40–54)	0.047[a]
WHtR, median (IQR), cm	0.59 (0.55–0.64)	0.58 (0.54–0.64)	0.58 (0.54–0.63)	0.59 (0.55–0.64)	0.059
WC, median (IQR), cm	95 (87–103)	94 (87–102)	94 (87–100)	95 (88–103)	0.124
BMI, median (IQR), kg/m^2	28 (26–31)	28 (25–31)	28 (26–31)	29 (25–32)	0.485
HDL-c, median (IQR), mmol/L	1.11 (0.93–1.29)	1.09 (0.93–1.32)	1.06 (0.88–1.22)	1.01 (0.85–1.22)	<0.001[b,c,d,e]
LDL-c, median (IQR), mmol/L	3.21 (2.63–3.75)	3.16 (2.61–3.78)	3.03 (2.50–3.57)	3.08 (2.58–3.70)	0.082
Triglycerides, median (IQR), mmol/L	2.33 (1.41–3.37)	2.18 (1.32–3.19)	2.10 (1.25–3.12)	2.08 (1.27–2.98)	0.120
Fasting glucose, median (IQR), mmol/L	5.05 (4.61–6.10)	5.05 (4.55–6.09)	5.11 (4.72–6.83)	5.05 (4.55–6.53)	0.331
SBP, median (IQR), mmHg	120 (110–132)	120 (110–130)	120 (110–133)	120 (110–130)	0.269
DBP, median (IQR), mmHg	80 (70–90)	80 (70–85)	80 (70–90)	80 (70–85)	0.114
Hypertension status, *n* (%)[f]	129 (23.7)	439 (26.6)	53 (29.4)	96 (25.3)	0.395
T2D status, *n* (%)	189 (28.3)	532 (27.1)	62 (28.3)	131 (29.0)	0.818
Hypoalphalipoproteinemia, *n* (%)	390 (58.5)	1149 (58.5)	138 (63)	322 (71.2)	<0.001

The four studied groups are the wild type genotype (denoted as −/−) in the two variants and the other groups included carriers on either one variant (denoted as +/− for carriers of rs2422493 but non-carriers of rs9282541 and −/+ in the reverse case) or in both (denoted as +/+)

IQR interquartile range, *WHtR* waist-to-height ratio, *WC* waist circumference, *BMI* body mass index, *HDL-c* high-density lipoprotein cholesterol, *LDL-c* low-density lipoprotein cholesterol, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *T2D* type 2 diabetes

[a] −/− vs. +/+, $p=0.035$

[b] −/− vs. −/+, $p=0.009$

[c] −/− vs. +/+, $p<0.001$

[d] −/+ vs. +/−, $p=0.002$

[e] +/− vs. +/+, $p<0.001$

[f] $n=2756$ patients

Path analysis

The hypothesized model fitted the data well (CFI = 1.0; TLI = 1.0; RMSEA = 0.0 90%CI (0.0, 0.04) (Fig. 1). After removing non-significant paths for improving parsimony, the fit indexes of the final model were CFI = 1.0; TLI = 1.0; RMSEA = 0.0 90% CI [0.0,0.02] (Fig. 2).

Type 2 diabetes

After adjusting for gender, age, HDL-c levels, WHtR, HOMA-IR, and ethnicity, we did not find any direct effect of any *ABCA1* group on T2D risk: $p=0.99$, $p=0.58$, and $p=0.91$ for groups +/−, −/+, and +/+ respectively (Table 2 and Fig. 2). Nevertheless, significant indirect effects from group −/+ and +/+ to T2D through HDL-c were found ($\beta=0.04$; $p=0.03$ and $\beta=0.06$; $p<0.01$, respectively). Meanwhile, the indirect effect of group +/− was not significant ($\beta\leq0.01$; $p=0.92$) meaning that people in group +/− were similarly prone to T2D as compared with the reference group. In contrast, rs9282541 carriers have a higher T2D risk through lower HDL-c concentrations than the wild-type group (Table 2 and Fig. 2). The difference between the indirect effects of −/+ and +/+ on T2D was not significant ($p=0.46$). However, we found two significant indirect effects from WHtR to T2D: one of them through HDL-c ($\beta=0.47$; $p=0.02$) and the other, through HOMA-IR before WHtR ($\beta=0.20$; $p<0.01$) (Table 2).

As expected, HDL-c concentrations were inversely associated with T2D risk ($\beta=-0.70$; $p<0.01$). In addition, male gender and age were also significantly associated ($p<0.01$). The standardized coefficients (βstand) suggest that HOMA-IR, age and HDL-c concentrations may have the strongest effects on T2D risk (βstand = 0.21, 0.20 and −0.19, respectively) (Table 2 and Fig. 2).

HDL-c

After adjusting for gender, age, WHtR, HOMA-IR, and ethnicity, the direct effect of −/+ and +/+ *ABCA1* groups on HDL-c concentrations were negative and significant in comparison to the reference group ($\beta=-0.06$; $p=0.03$ and $\beta=-0.08$; $p<0.01$, respectively) meaning that carriers of rs9282541 variant are likely to have lower levels of HDL-c than non-carriers. Insulin resistance measured with HOMA-IR was negatively associated with HDL-c ($\beta=-0.03$; $p<0.01$) (Table 2 and Fig. 2). Gender, age, and anthropometry were also significantly associated to HDL-c levels

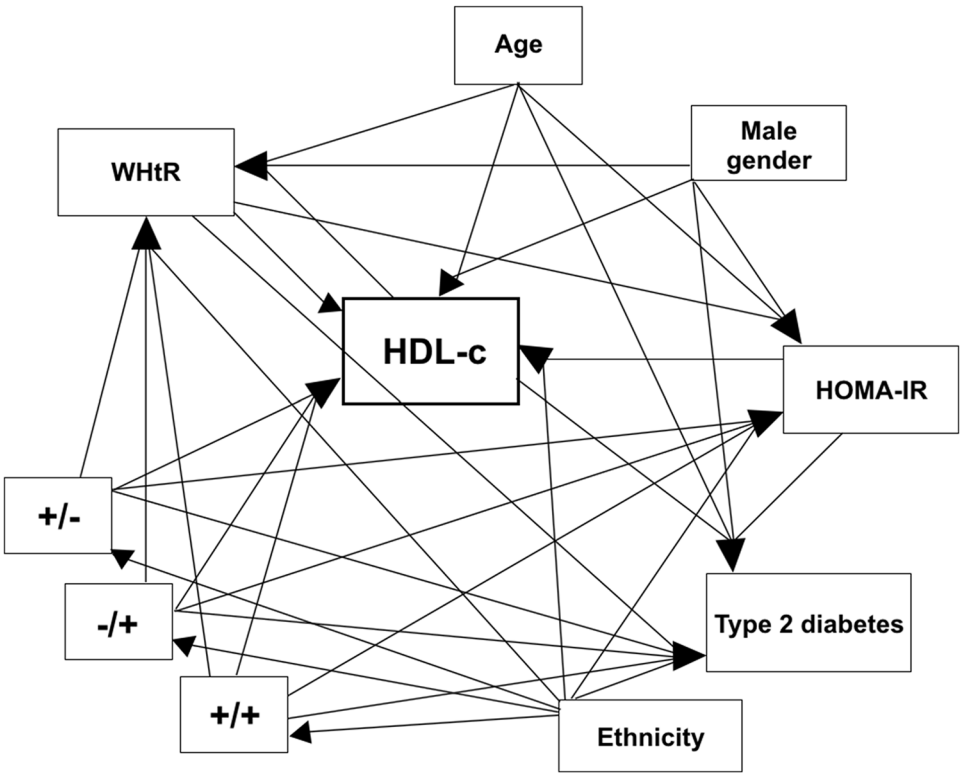

Fig. 1 Path diagram of the hypothesized causal relationships between *ABCA1* genotypes, age, gender, HOMA-IR, WHtR, ethnicity, HDL-c and T2D. The wild type genotype for both variants (denoted as −/−) was taken as reference group; the other groups included carriers of one variant (denoted as +/− for carriers of rs2422493 but non-carriers of rs9282541), carriers of the other variant (denoted as −/+ for non-carriers of rs2422493 but carriers of rs9282541) or carriers in both variants (denoted as +/+). *HDL-c* high-density lipoprotein cholesterol, *HOMA-IR* homeostatic model assessment for insulin resistance, *WHtR* waist-to-height ratio

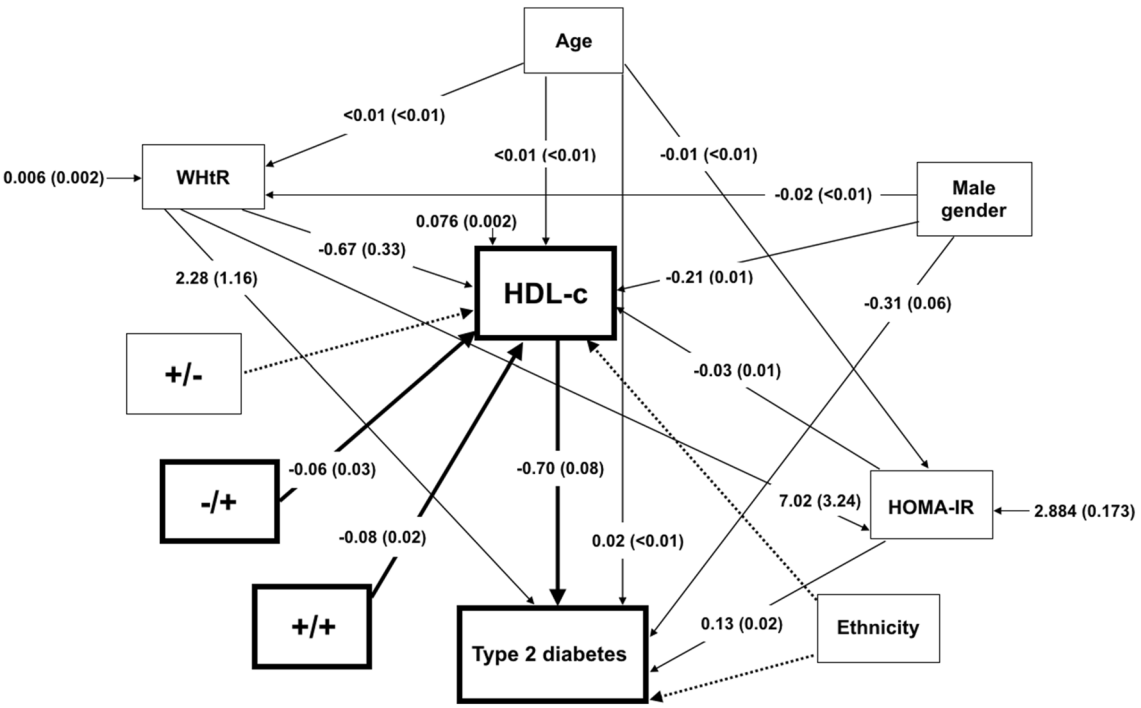

Fig. 2 Final path model presenting the causal relationships between *ABCA1* genotypes, age, gender, HOMA-IR, WHtR, ethnicity, HDL-c and T2D. The wild type genotype for both variants (denoted as −/−) was taken as reference group; the other groups included carriers of one variant (denoted as +/− for carriers of rs2422493 but non-carriers of rs9282541), carriers of the other variant (denoted as −/+ for non-carriers of rs2422493 but carriers of rs9282541) or carriers in both variants (denoted as +/+). Solid lines represent statistically significant effects; broken lines represent effects falling short of the conventional level of statistical significance $p < 0.05$. HDL-c and T2D were controlled by ethnicity. *HDL-c* high-density lipoprotein cholesterol, *HOMA-IR* homeostatic model assessment for insulin resistance, *WHtR* waist-to-height ratio

Table 2 Results of path analysis: direct and indirect effects of *ABCA1* genotypes, age, gender, HOMA-IR, WHtR on HDL-c, and T2D

Variables		Direct effects				Indirect effects		
		Standardized	Unstandardized	*p* value		Standardized	Unstandardized	*p* value
Dependent	Independent	beta	beta (SE)			beta	beta (SE)	
T2D	Male gender	−0.14	−0.31 (0.06)	< 0.001				
	HDL-c	−0.19	−0.70 (0.08)	< 0.001				
	HOMA-IR	0.21	0.13 (0.02)	< 0.001				
	WHtR	0.15	2.28 (1.16)	0.049				
					WHtR-> HDL-c-> T2D	0.03	0.47 (0.20)	0.022
					WHtR-> HOMA-IR-> HDL-c-> T2D	0.01	0.20 (0.05)	< 0.001
	Age	0.20	0.02 (< 0.01)	< 0.001				
	Ethnicity[a]	0.01	0.33 (0.61)	0.588				
	−/−		Reference[b]					
	+/−	< 0.01	< 0.01 (0.06)	0.999				
					+/− —> HDL-c-> T2D	< 0.01	< 0.01 (0.01)	0.916
	−/+	0.01	0.06 (0.10)	0.582				
					−/+ —> HDL-c-> T2D	0.01	0.04 (0.02)	0.033
	+/+	< 0.01	−0.01 (0.08)	0.909				
					+/+ —> HDL-c- > T2D	0.02	0.06 (0.02)	< 0.001
HDL-c	Male gender	−0.33	−0.21 (0.01)	< 0.001				
	HOMA-IR	−0.20	−0.03 (0.01)	< 0.001				
	WHtR	−0.17	−0.67 (0.33)	0.040				
	Age	0.06	< 0.01 (< 0.01)	0.007				
	Ethnicity[a]	−0.03	−0.25 (0.14)	0.078				
	−/−		Reference[b]					
	+/−	< 0.01	< 0.01 (0.01)	0.916				
	−/+	−0.05	−0.06 (0.03)	0.030				
	+/+	−0.09	−0.08 (0.02)	< 0.001				
HOMA-IR	Age	−0.07	−0.01 (< 0.01)	0.031				
	WHtR	0.32	7.02 (3.24)	0.031				
	−/−		Reference[b]					
	+/−	−0.02	−0.07 (0.09)	0.469				
	−/+	−0.02	−0.16 (0.15)	0.264				
	+/+	0.03	0.17 (0.13)	0.210				
WHtR	Male gender	−0.11	−0.02 (< 0.01)	< 0.001				
	Age	0.20	< 0.01 (< 0.01)	< 0.001				
	−/−		Reference[b]					
	+/−	−0.03	< 0.01 < 0.01)	0.217				
	−/+	−0.02	−0.01 (0.01)	0.268				
	+/+	0.02	0.01 (0.01)	0.293				

The four studied groups are the wild type genotype (denoted as −/−) in the two variants and the other groups included carriers on either one variant (denoted as +/− for carriers of rs2422493 but non-carriers of rs9282541 and −/+ in the reverse case) or in both (denoted as +/+)

T2D type 2 diabetes, *HDL-c* high-density lipoprotein cholesterol, *HOMA-IR* homeostatic model assessment for insulin resistance, *WHtR* waist-to-height ratio

[a]Principal components from two GWAS were used to estimate ethnicity, discriminating between American and European ancestry

[b]Reference was taken as the wild-type alleles of both single nucleotide polymorphisms of *ABCA1* gene

($p < 0.05$). According to the standardized coefficients, male gender has the strongest effect on HDL-c (βstand = −0.33; $p < 0.01$). The negative direction indicates that in average HDL-c concentrations were lower in men than in women. The second strongest effect found was for HOMA-IR (βstand = − 0.20; $p < 0.01$), indicating that insulin-resistant

individuals, in average, tend to have lower concentrations of HDL-c (Table 2 and Fig. 2).

We also tested indirect effects from genotype groups to HDL-c through HOMA-IR or WHtR but none of them were significant (data not shown).

HOMA-IR

We did not find any significant genetic effect on HOMA-IR among groups ($p = 0.47$ for +/–, $p = 0.26$ for −/+ and $p = 0.21$ for +/+ groups) (Table 2). Nevertheless, age ($\beta = -0.01$; $p = 0.03$) and WHtR ($\beta = 7.02$; $p = 0.03$) were associated to insulin resistance (Table 2 and Fig. 2).

WHtR

Regarding WHtR, we did not find any significant genetic effect ($p = 0.22$ for +/–; $p = 0.27$ for −/+; and $p = 0.29$ for +/+) (Table 2). However, significant effects were found for male gender and age ($\beta = -0.02$; $p < 0.01$ and $\beta < 0.01$; $p < 0.01$, respectively) (Table 2 and Fig. 2).

Discussion

To the best of our knowledge, this is the first study testing the combined effect of rs2422493 and rs9282541 *ABCA1* variants on HDL-c plasma levels and T2D risk. The promoter variant rs2422493 presumably causes a decreased transcriptional activity of the *ABCA1* gene in vivo, as shown through reporter gene studies in vitro. In atherosclerotic plaques, carriers of the T allele have lower *ABCA1* expression as demonstrated by Kyriakou et al. [16]. However, controversial results have been published regarding the effect of rs2422493 variant on HA. In the present study, neither HDL-c levels nor the HA frequency showed differences between carriers and non-carriers of rs2422493 variant, supporting the findings of published studies [16, 39], that included cohorts of White, Chinese, African-American and Hispanics [40]. In contrast, an Iranian study found that T carriers had a higher risk for HA, with lower HDL-c levels than the non-carriers [41]. The role of the rs2422493 SNP has been studied beyond the lipid profile, especially for cardiovascular disease. For instance, the presence of the T allele in −565C > T was associated to the development [42] and severity of atherosclerosis [43], as well as to coronary artery calcification [40].

Interestingly, we found a trend towards lower HDL-c when the four studied groups were analyzed, decreasing from the wild type genotype at both SNPs (−/−), carriers for the rs2422493 (+/–), carriers for rs9282541 (−/+) to carriers of both SNPs (+/+). Nevertheless, when we compared the direct effects on HDL-c between −/+ and +/+ groups, we did not find a significant difference. Moreover, the indirect effects of these groups on T2D through HDL-c were not statistically different, suggesting that the effects observed on HDL-c levels and on T2D risk are mainly driven by the R230C variant. Accordingly, when we analyzed carriers vs. non-carriers of rs9282541-T separately, we found that the direct effect on T2D was not significant ($\beta = 0.004$; $p = 0.94$), but the indirect effect through HDL-c was significant ($\beta = 0.05$; $p < 0.001$), corroborating our original results. This is in line with previous findings showing that the C230 allele of *ABCA1* is associated with increased risk for low HDL-c concentrations [10, 14], and the prevalence of HA among C230 carriers is greater than in non-carriers [10].

In the present study, we did not find a significant direct effect of any of the genetic groups on T2D. Similar results have been published previously for the rs9282541 variant. Miranda-Lora et al. did not find an association of this SNP with T2D in Mexicans even after adjusting for known risk factors [44]; neither did Campbell et al. in adults from Colombia of Native-American ancestry [45], nor Haghvirdizadeh et al., among Malaysians [46]. In contrast, Villarreal-Molina et al. identified a significant association between carriers of rs9282541 and early-onset T2D (≤45 years) in Mexican individuals, but such an association was lost in late-onset T2D group [13]. In the present study, we sought to systematically investigate the relationship between two *ABCA1* functional variants and T2D risk, as there are some conflicting results, mainly for the role of the R230C on T2D, possibly derived from the limited samples sizes used in previous studies [13], differences in the methodology to assess ethnicity, and possible influence of the functional variant −565C/T on T2D risk when present in combination with the R230C variant. Our results show for the first time, that the effect of R230C on T2D risk is indirect and through lowering HDL-c levels, a finding supported by a path analysis performed in a large cohort using robust methodology to assess and adjust for ethnicity in Mexican mestizos. Interestingly, when we assessed the direct and indirect effects of the analyzed variants according T2D age of onset we did not find any significant effect.

Importantly, we also tested indirect effects from all genetic groups to T2D through either WHtR or HOMA-IR but coefficients were not significant.

Our results suggest that the rs9282541 variant; regardless of rs2422493 genotype, increases T2D risk through lowering HDL-c levels. To the best of our knowledge, this is the first report on HDL-c concentrations as an intermediate risk factor between a functional *ABCA1* gene variant and T2D. This is in line with previous epidemiological studies that have identified HDL-c levels as a risk factor for T2D [23-25, 47]. According to our path analysis, WHtR has a direct and positive effect on T2D risk and insulin resistance (calculated

by HOMA-IR), and a negative effect on HDL-c, however neither of the studied *ABCA1* variants had any effect over WHtR. While contradictory association of the R230C variant has been reported with obesity (as determined by BMI), where some studies reported significant association [15], while other studies did not [48], in the present study we used WHtR instead of BMI, as it has been shown a better index associated with cardiovascular risk factors in different populations [31, 32], including Mexicans [49].

During the last years, in vitro, animal and clinical studies have uncovered a broad range of HDL actions contributing to the pathophysiology of T2D. Different studies suggest that lowering ABCA1 activity leads to impaired β-cell function [22, 50]. HDL may raise insulin secretion through an increase in cholesterol efflux, as has been proposed by Brunham et al. for the in vivo model of ABCA1 inactivation [51]. ApoAI and apoAII are considered two of the main components of the protein portion of HDL molecules which increase β-cell insulin secretion [27], presumably by two distinct mechanisms, the first one under high-glucose concentrations within the classical glucose-dependent metabolism pathway [27], and the second one, through a heterotrimeric G-protein-cAMP-protein kinase A-FoxO1-dependent mechanism [52] and the modulation of endoplasmic reticulum stress in β cells [53]. Furthermore, in a clinical trial using an infusion of reconstituted HDL (rHDL) in patients with T2D in a double-blind, placebo-controlled study, after four hours, plasma glucose levels decreased in rHDL group by two mechanisms, the first one through increasing plasma insulin levels, with higher β-cell function (evaluated by homeostasis model assessment beta cell function index), and the second one through the activation of AMP protein kinase in skeletal muscle [54]. Thus, the improvement of β-cells function through HDL can be observed in both in vitro as well as in vivo studies.

Our study identified carrier status of the rs9282541 polymorphism, male gender, insulin resistance, high WHtR, and advanced age as independent risk factors for low HDL-c plasma concentrations in Mexicans. In addition, for T2D we found HOMA-IR, age and HDL-c concentrations having the strongest effects on T2D risk, while indirect effects from WHtR to T2D were also identified, one through HDL-c and the other through HOMA-IR. However, when testing indirect effects from all *ABCA1* genetic groups for T2D through either WHtR or HOMA-IR, coefficients were not significant. Therefore, it will be of interest to test whether HDL modifies insulin secretion directly and to what extent the protein and/or lipid fraction of the HDL molecule or its subfractions influence insulin secretion and/or β-cell protection.

In conclusion, the present study shows the association between rs9282541 *ABCA1* gene variant and T2D risk, through lowering HDL-c concentrations. These results indicate that *ABCA1* functional variants might act as a heritable risk factor for T2D in Mexicans, through influencing HDL-c levels, putatively affecting cholesterol efflux and glucose homeostasis.

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Author contributions AO-G and HM-M designed, analyzed data and wrote the manuscript. DG-Q, OC-T, MLO-S, YS-K, VO, ED-D, LM-H, AG, and OP-M recollected patient's data and/or contributed to the manuscript. AZ-D and CAA-S designed and supervised the research and edited the manuscript. MTT-L designed, supervised the research and wrote the manuscript. MTT-L is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Compliance with ethical standards

Conflict of interest The authors declare that there are not competing conflicts of interest.

Ethical approval All procedures performed in human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments ethical standards. The study was approved by The Committee of Ethics and the Institutional Review Board of the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán (INCMNSZ).

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