










RESEARCH ARTICLE

ABO gene polymorphisms are associated with acute coronary syndrome and with plasma concentration of HDL-cholesterol and triglycerides

Gilberto Vargas-Alarcón ^{1#}, Oscar Pérez-Méndez ^{1#}, Rosalinda Posadas-Sánchez ², Héctor González-Pacheco ³, Alexandra Arias-Mendoza ³, Galileo Escobedo ⁴, Teresa Juárez-Cedillo ⁵, Marva Arellano-González ¹, and José Manuel Fragoso ^{1*}

The role of *ABO* gene polymorphisms in acute coronary syndrome (ACS) and lipid metabolism is increasingly recognized. We investigated whether *ABO* gene polymorphisms are significantly associated with ACS and the plasma lipid profile. Six *ABO* gene polymorphisms (rs651007 T/C, rs579459 T/C, rs495928 T/C, rs8176746 T/G, rs8176740 A/T, and rs512770 T/C) were determined by 5' exonuclease TaqMan assays in 611 patients with ACS and 676 healthy controls. The results demonstrated that the rs8176746 T allele was associated with a lower risk of ACS under the co-dominant, dominant, recessive, over-dominant, and additive models ($P = 0.0004$, $P = 0.0002$, $P = 0.039$, $P = 0.0009$, and $P = 0.0001$, respectively). Furthermore, under co-dominant, dominant, and additive models, the rs8176740 A allele was associated with a lower risk of ACS ($P = 0.041$, $P = 0.022$, and $P = 0.039$, respectively). On the other hand, the rs579459 C allele was associated with a lower risk of ACS under the dominant, over-dominant, and additive models ($P = 0.025$, $P = 0.035$, and $P = 0.037$, respectively). In a subanalysis performed with the control group, rs8176746 T and rs8176740 A alleles were associated with low systolic blood pressure and with both high high-density lipoprotein-cholesterol (HDL-C) and low triglyceride plasma concentrations, respectively. In conclusion, *ABO* gene polymorphisms were associated with a lower risk of ACS, and lower systolic blood pressure and plasma lipid levels, suggesting a causal relationship between ABO blood groups and the incidence of ACS.

Keywords: Polymorphisms, acute coronary syndrome (ACS), human ABO blood group system.

Introduction

Acute coronary syndrome (ACS) is characterized by a partial or total thrombotic obstruction of coronary artery caused by the rupture or erosion of atherosclerotic plaque. ACS is a set of clinical complications, including unstable angina and myocardial infarction with or without ST-segment elevation [1, 2]. This syndrome is multifactorial, resulting from the combination of genetic background and cardiovascular risk factors, such as obesity, dyslipidemia, and hypertension, among others, that play an important role in the development of atherosclerotic plaque [1–4]. In the last years, the association between ABO blood groups and plasma lipid levels has shown that carriers of non-O type had higher levels of total cholesterol, and low-density lipoprotein cholesterol (LDL-C), leading to early development of cardiovascular diseases [5–7]. The ABO blood groups are encoded by the ABO gene located at q34.2 of chromosome 9. Recent studies have established the

association of six genetic variants of the *ABO* gene with a high prevalence of different cardiovascular diseases, including ACS, in different populations, the rs579459 T/C, rs8176746 T/G, rs512770 T/C, rs495928 T/C, rs651007 T/C, and rs8176740 A/T [7–17]. However, the association of *ABO* gene polymorphisms with ACS is still controversial and merits to be further explored.

Considering the potential impact of ABO groups on cardiovascular diseases, we hypothesized that the *ABO* gene polymorphisms are associated with the incidence of ACS, and with plasma lipid profile in the Mexican population. To explore this possibility, the present study aimed to establish whether the *ABO* rs651007 T/C, rs579459 T/C, rs495928 T/C, rs8176746 T/G, rs8176740 A/T, and rs512770 T/C polymorphisms are associated with the risk of developing ACS. In addition, we evaluated whether these polymorphisms are associated with plasma lipid profile.

¹Departamento de Biología Molecular, Instituto Nacional de Cardiología Ignacio Chávez, Mexico City, México; ²Departamento de Endocrinología, Instituto Nacional de Cardiología Ignacio Chávez, Mexico City, México; ³Unidad Coronaria, Instituto Nacional de Cardiología Ignacio Chávez, Mexico City, México; ⁴Unidad de Medicina Experimental, Hospital General de Mexico, Dr. Eduardo Liceaga, Mexico City, México; ⁵Unidad de Investigación en Epidemiología y Servicios de Salud-Área de Envejecimiento. Centro Médico Nacional Siglo XXI. Instituto Mexicano del Seguro Social, Mexico City, México.

*Correspondence to José Manuel Fragoso: mfragoso1275@yahoo.com.mx

#Gilberto Vargas-Alarcón and Oscar Pérez-Méndez contributed equally to this work.

DOI: 10.17305/bb.2023.9244

© 2023 Vargas-Alarcón et al. This article is available under a Creative Commons License (Attribution 4.0 International, as described at <https://creativecommons.org/licenses/by/4.0/>).

Table 1. Information of the studied polymorphism tested

Gene ^a symbol	dbSNP ^a	Chromosome (NCBI Build 156) ^a	Position (NCBI Build 156) ^a	Change base (pb)	Location in gene ^a	Tagged ABO blood group
ABO	rs651007	9q34.2	133278431	T > C	5'-UTR	A
ABO	rs579459	9q34.2	133278724	C > T	5'-UTR	A
ABO	rs495828	9q34.2	133279294	T > G	5'-UTR	O
ABO	rs8176746	9q34.2	133255935	T > G	Exon 7	B
ABO	rs8176740	9q34.2	133256085	T > A	Exon 7	A
ABO	rs512770	9q34.2	133258116	T > C	Exon 5	O

^aThe chromosomal location for each SNP table was obtained by querying each SNP “rs” number in the NCBI single nucleotide polymorphism database (dbSNP), build 156 on the 21st of September 2022 (<http://www.ncbi.nlm.nih.gov/projects/SNP/>).

Materials and methods

Characteristics of the study population

We included 1287 Mexican mestizo individuals, 611 patients with ACS, and 676 healthy controls. The sample size was calculated for an unmatched case-control study with a power of 80% and an alpha error of 0.05 (<http://www.openepi.com/SampleSize/SSCC.html>). From July 2015 to May 2018, 611 patients with ACS (81.5% men and 18.5% women, with a mean age of 57.7 ± 9.9 years) were referred to the Instituto Nacional de Cardiología Ignacio Chávez. The diagnosis of ACS was made following the European Society of Cardiology (ESC) and American College of Cardiology (ACC) definitions [18, 19]. Clinical characteristics, electrocardiographic changes, and biochemical markers (creatinine phosphokinase isoenzymes, troponin I) were determined for diagnosis. The control group included 676 healthy individuals (66.4% men and 33.5% women, with a mean age of 54.0 ± 7.7 years) that were recruited from the cohort of Genetics of Atherosclerosis Disease (GEA) Mexican study database [20]. Control subjects were asymptomatic and apparently healthy without clinical or family history of premature coronary artery disease (CAD), congestive heart failure, liver, renal, thyroid, or oncological disease. In addition, control subjects had a coronary calcium score of zero determined by computed tomography, indicating the absence of subclinical atherosclerosis in these individuals [20]. The association of ABO gene polymorphisms with plasma lipid levels was evaluated only in controls. All the included subjects were ethnically matched and considered Mexican mestizos only if they and their ancestors (at last three generations) were born in Mexico.

Laboratory analyses

Cholesterol and triglyceride plasma concentrations were determined by enzymatic/colorimetric assays (Randox Laboratories, Crumlin, UK). High-density lipoprotein-cholesterol (HDL-C) plasma concentrations were determined by the phosphotungstic acid-Mg²⁺ method. LDL-C concentrations were calculated in samples with triglyceride concentrations lower than 400 mg/dL using Friedewald’s formula [21]. Dyslipidemia was defined as the presence of one or more of the following conditions: cholesterol > 200 mg/dL, LDL-C > 130 mg/dL, HDL-C < 40 mg/dL, or triglycerides > 150 mg/dL, according

to the guidelines of the National Cholesterol Education Project (NCEP) Adult Treatment Panel (ATP III) (<https://www.nhlbi.nih.gov/resources/third-report-expert-panel-detection-evaluation-and-treatment-high-blood-cholesterol-0> [accessed on May 2, 2023]). According to the MSD manual guidelines, type 2 diabetes mellitus (T2DM) was considered when participants had a fasting glucose level ≥ 126 mg/dL, previously diagnosed by a physician (<https://www.msmanuals.com/professional/endocrine-and-metabolic-disorders/diabetes-mellitus-and-disorders-of-carbohydrate-metabolism/diabetes-mellitus-dm/#v29299021> [accessed on May 2, 2023]). Hypertension was defined by a systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or the use of oral antihypertensive therapy.

Genetic analysis

DNA extraction was performed from total blood as previously described [22]. The determination of the ABO 5'UTR rs651007 T/C, ABO 5'UTR rs579459 T/C, ABO 5'UTR rs495928 T/C, ABO Leu266Met rs8176746 T/G, ABO Phe216Ile rs8176740 A/T, and ABO Pro74Ser rs512770 T/C polymorphisms were performed using 5'exonuclease TaqMan assays on a 7900HT Fast Real-Time PCR system in accordance with manufacturer’s instructions (Applied Biosystems, Foster City, USA) (Table 1). As a quality control, 10% of the samples were genotyped twice; results were concordant for all cases.

Ethical statement

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics and Research Committees of Instituto Nacional de Cardiología Ignacio Chávez (protocol number: 22-1288, approved: 08/February/2022). Informed consent was obtained from all subjects involved in the study.

Statistical analysis

Gene frequencies of ABO polymorphisms in patients and controls were obtained by direct counting. The Hardy-Weinberg equilibrium was evaluated in patients with ACS and individual controls by chi-squared test. Data analysis was performed with SPSS program version 18.0 (IBM, Chicago, IL). Either Mann-Whitney U or Student’s *t*-test was performed to compare the continuous variables. For categorical variables, chi-squared

Table 2. Demographic, clinical, and biochemical parameters of the studied individuals

Characteristics		ACS patients (n = 611)	Healthy controls (n = 676)	P-value
Age (years)		57.7 ± 9.9	54.3 ± 7.6	<0.001
Gender, n (%)	Male	498 (81.5)	449 (66.4)	<0.001
	Female	113 (18.5)	227 (33.5)	
BMI (kg/m ²)		27 [25–29]	28 [26–31]	0.09
Blood pressure (mmHg)	Systolic	130 [114–144]	115 [106–126]	<0.001
	Diastolic	80 [70–90]	72 [66–77]	<0.001
Glucose (mg/dL)		127 [101–188]	91 [84–99]	<0.001
Total cholesterol (mg/dL)		163 [127–198]	188 [164–210]	<0.001
HDL-C (mg/dL)		37 [32–45]	42 [35–52]	<0.001
LDL-C (mg/dL)		103 [75–132]	115 [94–134]	<0.001
Triglycerides (mg/dL)		148 [109–199]	152 [112–209]	0.166
Hypertension, n (%)	Yes	345 (56)	202 (30)	<0.001
Type 2 diabetes mellitus, n (%)	Yes	214 (35)	64 (9)	<0.001
Dyslipidemia, n (%)	Yes	522 (85)	481 (71)	<0.001
Smoking, n (%)	Yes	216 (35)	149 (22)	<0.001

Data are expressed as median or interquartile interval [25th–75th], n (% of total patients), or mean ± SD. P values were estimated using Student's t-test or Mann–Whitney U-test for continuous variables and chi-square test for categorical values. BMI: Body mass index; HDL-C: High-density lipoprotein-cholesterol; LDL-C: Low-density lipoprotein-cholesterol; ACS: Acute coronary syndrome.

or Fisher's exact test was used. The analysis association of the rs651007 T/C, rs579459 T/C, rs495928 T/C, rs8176746 T/G, rs8176740 A/T, and rs512770 T/C single nucleotide polymorphisms (SNPs) with the risk of ACS was performed under the following inheritance models: additive, which compares the subgroup of homozygotes subjects carrying the major allele with heterozygotes as well as with the minor allele homozygotes; codominant, which compares the subgroup of homozygous individuals carrying the major allele with homozygotes of the minor allele; dominant, which compares the subgroup of homozygous individuals carrying the minor allele with the subgroup conformed by heterozygotes and major allele homozygotes; heterozygous, which compares the subgroup conformed by homozygotes carrying major allele and homozygotes carrying minor allele vs heterozygotes; recessive, which compares the subgroup conformed by heterozygotes and major allele homozygotes vs homozygotes of the minor allele. These analyses were performed by a logistic regression, adjusted for cardiovascular risk factors, and determined whether the presence of the genetic variant is associated with the occurrence of the disease [23, 24]. The Bonferroni test was used to correct the P values (P) according to the number of tests per SNP based on the different models of inheritance. The values of $P < 0.05$ were considered statistically significant, and all odds ratios (OR) were presented as 95% confidence intervals. For the subset of controls grouped by genotypes, the plasma lipid concentrations were expressed as means ± SD, and comparisons were performed by ANOVA and F-test. P values < 0.05 were considered statistically significant. The statistical power to

detect an association of the polymorphisms with ACS was 0.80 according to the OpenEpi software (<http://www.openepi.com/SampleSize/SSCC.html> [accessed on 17 June 2021]).

Linkage disequilibrium analysis (LD, D') and haplotype design were performed using Haploview version 4.1 (Broad Institute of Massachusetts Institute of Technology and Harvard University, Cambridge, MA, USA). This software analyzes the combination of alleles in a single gene, or alleles in multiple genes along a chromosome that tend to be inherited together due to their chromosomal proximity, providing the statistical calculation of LD, D', logarithm of the odds (LOD) and r-squared, as well as possible haplotype patterns from primary genotypes, using the Human Haplotype Map project data [25].

Results

Characteristics of the study sample

Demographic, clinical, and biochemical parameters of the ACS patients and healthy controls are presented in Table 2. There were significant differences between the ACS patients and healthy controls. As expected, traditional risk factors of cardiovascular diseases were altered in ACS patients; glucose plasma levels and blood pressure, frequency of hypertension, dyslipidemia, and smoking habit were higher in patients than in controls. Conversely, the total cholesterol, and LDL-C concentrations in ACS patients were lower than those in the control group; this effect is associated to their anti-dyslipidemic treatment, and changes of lifestyle after the clinical event.

Table 3. Association of ABO polymorphisms with ACS accordance to the inheritance models

Polymorphic site (rsID-number)	Model	Genotype	ACS patient, n = 611 (n[%])	Controls, n = 676 (n[%])	OR (95%CI)	P-value
rs8176746	Co-dominant	GG	540 (0.884)	555 (0.821)	0.17 (0.03–0.97)	0.0004
		GT	69 (0.113)	112 (0.166)		
		TT	2 (0.003)	9 (0.013)		
	Dominant	GG	540 (0.884)	555 (0.821)	0.49 (0.34–0.72)	0.0002
		GT + TT	71 (0.116)	121 (0.179)		
Recessive	GG + GT	609 (0.997)	667 (0.987)	0.19 (0.03–1.06)	0.039	
	TT	2 (0.003)	9 (0.013)			
Over-dominant	GG + TT	542 (0.887)	564 (0.834)	0.53 (0.36–0.77)	0.0009	
	GT	69 (0.113)	112 (0.166)			
Additive	–	–	–	–	0.50 (0.35–0.71)	0.0001
rs8176740	Co-dominant	TT	180 (0.294)	167 (0.247)	0.69 (0.49–1.00)	0.041
		TA	296 (0.484)	332 (0.492)		
		AA	135 (0.221)	176 (0.261)		
	Dominant	TT	180 (0.295)	167 (0.247)	0.71 (0.53–0.95)	0.022
		TA + AA	431 (0.705)	508 (0.753)		
Recessive	TT + TA	476 (0.779)	499 (0.739)	0.90 (0.65–1.21)	0.479	
	AA	135 (0.221)	176 (0.261)			
Over-dominant	TT + AA	315 (0.515)	343 (0.508)	0.83 (0.64–1.07)	0.149	
	TA	296 (0.485)	332 (0.492)			
Additive	–	–	–	–	0.84 (0.70–1.00)	0.039
rs579459	Co-dominant	TT	438 (0.717)	445 (0.659)	0.75 (0.53–0.97)	0.081
		TC	157 (0.257)	200 (0.296)		
		CC	16 (0.026)	30 (0.044)		
	Dominant	TT	438 (0.717)	445 (0.659)	0.72 (0.54–0.96)	0.025
		TC + CC	173 (0.283)	230 (0.341)		
Recessive	TT + TC	595 (0.974)	645 (0.956)	0.82 (0.40–1.71)	0.599	
	CC	16 (0.026)	30 (0.044)			
Over-dominant	TT + CC	454 (0.743)	475 (0.704)	0.73 (0.54–0.98)	0.035	
	TC	157 (0.257)	200 (0.296)			
Additive	–	–	–	–	0.77 (0.60–0.99)	0.037

The P-values were calculated by the logistic regression analysis, and ORs were adjusted for gender, age, blood pressure, BMI, glucose, total cholesterol, HDL-C, triglycerides, and smoking habit. Bold: $P < 0.05$; ACS: Acute coronary syndrome; OR: Odds ratio; CI: Confidence interval.

Association of ABO polymorphisms with ACS

Allele and genotype frequencies of the polymorphic sites in patients with ACS and controls were in Hardy–Weinberg equilibrium. In the first analysis, the genetic distribution of the rs512770 T/C, rs651007 T/C, and rs495928 T/C, polymorphisms were similar in patients with ACS and healthy controls. Nonetheless, rs8176746 T/G, rs8176740 A/T, and rs579459 T/C genotype frequencies showed significant differences between ACS patients and healthy individuals ($P < 0.05$) (Table S1). In addition, the association analysis showed that under different models, the T allele and TT genotype of the rs8176746 T/G polymorphism were associated with decreased risk of developing ACS (OR = 0.17, 95%CI: 0.03–0.97, $P_{\text{Co-dominant}} = 0.0004$, OR = 0.49, 95%CI: 0.34–0.72, $P_{\text{Dominant}} = 0.0002$, OR = 0.19, 95%CI: 0.03–1.06, $P_{\text{Recessive}} = 0.039$, OR = 0.53, 95%CI: 0.36–0.77, $P_{\text{Over-dominant}} = 0.0009$, and OR = 0.50, 95%CI: 0.35–0.71, $P_{\text{Additive}} = 0.0001$, respectively). In addition, the A allele and AA genotype of the rs8176740 A/T polymorphism

was associated with a lower risk of developing ACS (OR = 0.69, 95%CI: 0.49–1.00, $P_{\text{Co-dominant}} = 0.041$, OR = 0.71, 95%CI: 0.53–0.95, $P_{\text{Dominant}} = 0.022$, and OR = 0.84, 95%CI: 0.70–1.00, $P_{\text{Additive}} = 0.039$, respectively). Finally, the C allele and CC genotype of the rs579459 T/C polymorphism were associated with decreased risk of developing ACS (OR = 0.72, 95%CI: 0.54–0.96, $P_{\text{Dominant}} = 0.025$, OR = 0.73, 95%CI: 0.54–0.98, $P_{\text{Over-dominant}} = 0.035$, and OR = 0.77, 95%CI: 0.60–0.99, $P_{\text{Additive}} = 0.037$, respectively) (Table 3). All models were adjusted for gender, age, blood pressure, BMI, glucose, total cholesterol, HDL-C, triglycerides, and smoking habit. Associations of ABO genotypes with ACS remained essentially the same according to the genetic models when data were analyzed without adjustment by traditional risk factors (Table S2).

Linkage disequilibrium analysis

There was a moderate linkage disequilibrium ($D' \geq 0.80$) between the rs8176746 T/G, rs8176740 A/T, rs512770 T/C,

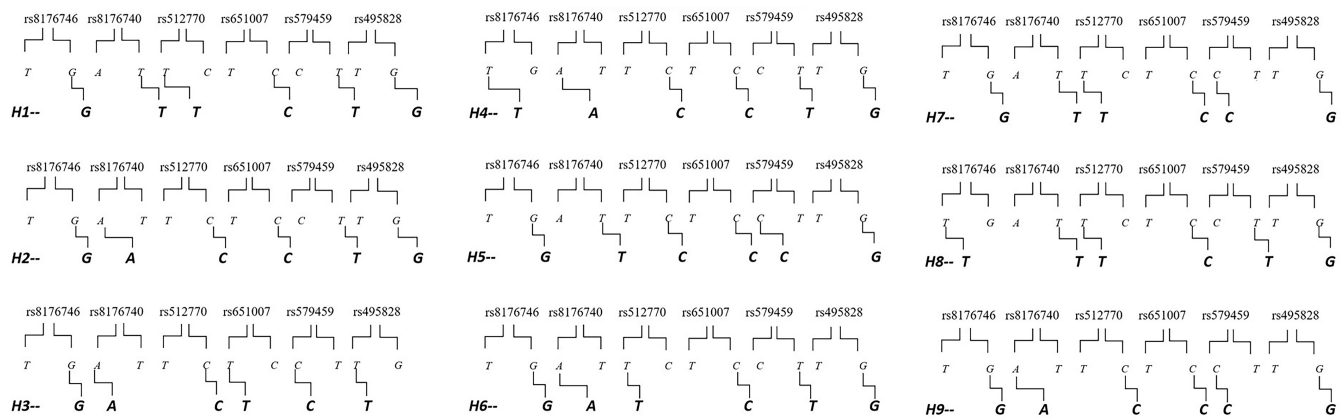


Figure 1. Scheme depicting the combination of alleles that integrates the nine haplotypes designed by Haploview based on human Haplotype Map project data. The nomenclature used in the manuscript, H1–H9, is indicated at the bottom of each haplotype.

Table 4. Distribution of ABO haplotypes in ACS patients and healthy controls

Polymorphic site (rsID-number)	ACS patients, <i>n</i> = 608	Healthy controls, <i>n</i> = 675	OR	95%CI	<i>P</i> -value
rs8176746 T/G–rs8176740 A/T–rs512770 T/C–rs651007 T/C–rs579459 C/T–rs495828 T/G	Hf	Hf			
H1 (GTTCTG)	0.486	0.433	1.24	1.06–1.44	0.007
H2 (GACCTG)	0.260	0.255	1.03	0.85–1.22	0.769
H3 (GACTCT)	0.129	0.121	1.07	0.85–1.36	0.538
H4 (TACCTG)	0.048	0.060	0.79	0.56–1.12	0.190
H5 (GTCCTG)	0.028	0.008	3.73	1.83–7.6	0.0001
H6 (GATCTG)	0.005	0.027	0.18	0.07–0.43	0.0001
H7 (GTTCCG)	0.006	0.025	0.23	0.10–0.52	0.0001
H8 (TTTCTG)	0.003	0.020	0.16	0.06–0.48	0.0001
H9 (GACCCG)	0.004	0.016	0.26	0.10–0.69	0.0037

The polymorphism order of haplotypes is according to the position in the chromosome. (rs8176746–rs8176740–rs512770–rs651007–rs579459–rs495828 chromosome 9q34.2). Bold: *P* < 0.05; Hf: Haplotype frequency.

rs651007 T/C, rs579459 T/C, and rs495828 T/C polymorphisms. In addition, this analysis showed six of nine haplotypes (H1–GTTCTG, H5–GTCCTG, H6–GATCTG, H7–GTTCCG, H8–TTTCTG, and H9–GACCCG, Figure 1) with important differences between the two groups. (Table 4). The H1 and H5 haplotypes were associated with a higher risk of developing ACS (OR = 1.24, 95%CI: 1.06–1.44, *p*C = 0.007, and OR = 3.73, 95%CI: 1.83–7.6, *p*C = 0.001, respectively), whereas the H6, H7, H8, and H9 haplotypes were associated with a low risk of developing ACS (OR = 0.18, 95%CI: 0.07–0.43, *p*C = 0.0001, OR = 0.23, 95%CI: 0.10–0.52, *p*C = 0.0001, OR = 0.16, 95%CI: 0.06–0.48, *p*C = 0.0001, and OR = 0.26, 95%CI: 0.10–0.69, *p*C = 0.0037, respectively).

ABO polymorphisms and plasma lipids concentrations

Previous reports have suggested that the ABO blood groups are associated with plasma lipid levels [5–7]. To estimate the potential effect of rs8176746 T/G, rs8176740 A/T, and rs579459

T/C polymorphisms, we compared plasma lipids concentrations (total cholesterol, LDL-C, HDL-C, and triglycerides), as well as BMI, blood pressure, and glucose in individuals grouped by genotypes of the three studied polymorphisms (Table 5). For this analysis, we only included the healthy controls group; patients were excluded from this subanalysis because their lipid concentrations were altered by the use of anti-dyslipidemic or anti-hypertensive drugs [26–28]. Interestingly, subjects with the rs8176746 TT genotype had lower systolic blood pressures (110 [105–116] mmHg) compared with carriers of either GT (120.5 [109–129] mmHg) or GG genotypes (115 [105–125] mmHg) (*P* = 0.034). On the other hand, individuals with rs8176740 AA genotype showed higher concentrations of HDL-C (45 [37.2–53.3] mg/dL) than subjects with either TA or TT genotypes (Table 5). In addition, individuals with rs8176740 AA genotype showed lower concentrations of triglycerides (138 [107–186.5] mg/dL) when compared to TA (155 [112.6–223] mg/dL) or TT genotype (171 [117.7–208.8] mg/dL). The rs579459

Table 5. Distribution of plasma lipid concentrations according to the different genotypes in healthy control group (n = 676)

ABO	rs8176746 T/G			P-value*
	GG (n = 555)	GT (n = 112)	TT (n = 9)	
<i>Parameters</i>				
BMI (kg/m ²)	28.17 [25.6–30.7]	27.5 [25.7–29.9]	30.8 [27.7–31.6]	0.115
Blood pressure (mmHg)				
Systolic	115 [106–125]	120.5 [109–129]	110 [105–116]	0.034
Diastolic	72 [66–77]	73.5 [68.5–79.5]	70 [67–75.5]	0.489
Glucose (mg/dL)	90 [84–98]	93.5 [85–102]	87 [84–108]	0.666
Total cholesterol (mg/dL)	187.9 [164–210]	188 [166–207]	186 [166–200]	0.504
HDL-C (mg/dL)	42.9 [35.1–53.6]	41 [35.1–48.9]	39.7 [34.5–41.2]	0.255
LDL-C (mg/dL)	115 [93.7–134.2]	114.5 [93.7–131.6]	117 [97.6–133]	0.856
Triglycerides (mg/dL)	151 [112–207]	154 [111–225]	161 [122.4–203.6]	0.837
ABO	rs8176740 A/T			P-value
	TT (n = 167)	TA (n = 332)	AA (n = 176)	
<i>Parameters</i>				
BMI (kg/m ²)	27.7 [25–30.8]	28 [25.7–30.7]	27.7 [25–30.8]	0.292
Blood pressure (mmHg)				
Systolic	115 [107–124]	115 [105–127]	116.5 [108–127]	0.604
Diastolic	72 [66.7–76.5]	72 [66–77.5]	72.5 [66.8–78]	0.438
Glucose (mg/dL)	91 [84–99]	91 [84–99.2]	90 [84–98]	0.521
Total cholesterol (mg/dL)	185 [163.3–205]	190 [165–213]	189 [165.6–207]	0.499
HDL-C (mg/dL)	40 [34.1–50.0]	41.5 [34.6–53.5]	45 [37.2–53.3]	0.036
LDL-C (mg/dL)	113 [93.5–131.6]	117 [93.8–136.3]	115 [94.3–132.4]	0.898
Triglycerides (mg/dL)	171 [117.7–208.8]	155 [112.6–223]	138 [107–186.5]	0.007
ABO	rs579459 T/C			P-value
	TT (n = 445)	TC (n = 200)	CC (n = 30)	
<i>Parameters</i>				
BMI (kg/m ²)	27.9 [25.8–30.5]	28.2 [25.4–30.7]	27.8 [24.2–31.6]	0.955
Blood pressure (mmHg)				
Systolic	115 [106–126]	116.5 [107–128]	114 [105–124]	0.429
Diastolic	72 [66.5–77]	73 [67–78]	68 [62–76]	0.157
Glucose (mg/dL)	90 [84–99]	92 [84–99.2]	86 [83–93]	0.382
Total cholesterol (mg/dL)	187 [163–207.6]	193 [165.9–215]	196 [176.8–215]	0.087
HDL-C (mg/dL)	42 [35.2–52.1]	42 [34.9–53]	42 [38.8–57]	0.368
LDL-C (mg/dL)	112 [92.9–131.7]	119 [99.6–136.9]	124 [93–139]	0.424
Triglycerides (mg/dL)	151 [112.8–205.6]	154 [113–223.3]	155 [95.5–182]	0.627

Data of BMI, blood pressure, glucose, total cholesterol, HDL-C, LDL-C, and triglycerides are expressed as mean ± SD. Bold: P < 0.05; *: ANOVA test; BMI: Body mass index; HDL-C: High-density lipoprotein-cholesterol; LDL-C: Low-density lipoprotein-cholesterol.

T/C polymorphism was not associated with total cholesterol, LDL-C, HDL-C, triglycerides, BMI, blood pressure, or glucose (Table 5).

Discussion

In the present study, we studied six polymorphisms (rs651007 T/C, rs579459 T/C, rs495928 T/C, rs8176746 T/G, rs8176740 A/T, and rs512770 T/C) located in the ABO gene that have been previously implicated in plasma lipids concentrations in CAD [7–17]. In our study, we reported that the rs579459 C,

rs8176746 T, and rs8176740 A alleles confer a low risk of ACS. We also found that the H1 and H5 haplotypes were associated with a high risk of developing ACS, whereas the H6, H7, H8, and H9 haplotypes were associated with a low risk. Interestingly, the haplotypes H6 to H9 include the rs579459 C, rs8176746 T, and rs8176740 A alleles that conferred low ACS risk. Importantly, the associations of ABO genotypes remained significant even when data were not adjusted by traditional risk factors (Table S2). To the best of our knowledge, our work is one of the few studies that describe the association of these polymorphisms with ACS. The association of the rs579459 T/C,

rs8176746 T/G, and rs8176740 A/T polymorphisms with cardiovascular diseases and ACS in different populations is scarce and controversial. In contrast with our findings, Zhao et al. [11] reported that the CC genotype of the rs579459 T/C increased the risk of CAD and was related to a higher risk of major adverse cardiovascular events in the Chinese population. Wauters et al. [16] reported that the rs579459 C allele was associated with recurrent myocardial infarction, and cardiac death in a cohort of patients with ACS. In line with these data, Paquette et al. [7] reported that rs579459 C and rs8176746 T alleles increased the risk of developing cardiovascular disease in the Caucasian population with familial hypercholesterolemia. In the same way, Groot et al. [17] reported that the rs8176746 TT genotype increased the risk of thromboembolic events, and myocardial infarction in the Caucasian population. In addition, Li and Schooling [13] reported that the T allele of the rs8176746 T/G SNP is associated with the risk of developing some diseases of the circulatory system, such as ischemia heart disease, myocardial infarction, and major coronary heart disease event. In contrast, Gao et al. [14] reported that the rs579459 T allele was associated with the highest risk of developing coronary heart disease in Asian population. Even if controversial, our data and previous reports suggest an association of the rs579459 T/C, rs8176746 T/G, and rs8176740 A/T SNPs with cardiovascular events. The potential mechanisms that could explain the statistical association of ABO polymorphisms with cardiovascular outcomes may involve the gut microbiota and platelets aggregation [8, 29–34]. First, A, B, and H carbohydrates are expressed in different tissues and may also be secreted as soluble molecules in certain individuals. The absence of N-acetyl galactosamine transferase activity necessary to structure A antigen, alters gut microbiota in pigs [29]. Also, the secretion of soluble A- and B-antigens seems to affect gut microbiota in humans [30–32]. In this context, gut dysbiosis has related to CAD risk factors, such as obesity, diabetes, dyslipidemia, hypertension, uric acid metabolism, and oxidative stress [33]. Therefore, the association of ABO polymorphisms with ACS observed in this study may be mediated by microbiota. Second, A, B, and H carbohydrates are expressed on different glycoproteins on platelet surfaces and are also present on glycans of the von Willebrand factor [34]. Consequently, ABO group determinants may affect the thrombotic process during a coronary event.

It should be emphasized that the frequency of these polymorphisms varies according to the ethnic origin of the study populations. Here, we reported that the frequency of the rs579459 C, rs8176746 T, and rs8176740 A alleles in the Mexican population were 19.2%, 9.6%, and 50.6%, respectively (Supplementary Table 1). According to data obtained from National Center for Biotechnology Information (NCBI) (<https://www.ensembl.org/index.html> [accessed on 17 January 2022]), the distribution of the rs579459 C allele in our population, as well as in the Caucasian and Asian populations was similar (19.2%, 21%, and 19%, respectively). Mexican (from Los Angeles) and African individuals showed a low frequency of this allele (14.1%, and 13%, respectively). Concerning the rs8176746 T allele, in our study, in individuals from Los Angeles

with Mexican ancestry, as well as in Caucasian, the frequency of this polymorphism was low (9.6%, 8%, and 8%, respectively), whereas Asian and African individuals have a higher frequency of this allele (19% and 17%, respectively). Finally, the individuals from Los Angeles with Mexican ancestry, as well as the population in this study, have a low frequency of the rs8176740 A allele (59.4 and 50.6%, respectively) compared with Caucasian, Asian, and African individuals (78%, 71%, and 76%, respectively) (<https://www.ensembl.org/index.html> [accessed on June 02, 2023]). Considering our results and the different distribution of the ABO polymorphisms, we propose that additional studies in other populations with different ethnic origins could help to define the true role of these polymorphisms in the risk of developing ACS.

To explore whether ABO genotypes contribute to ACS incidence via plasma lipid levels, we determined the effect of the rs579459 T/C, rs8176746 T/G, and rs8176740 A/T polymorphisms on plasma lipid concentrations and some cardiovascular risk factors. We found that individuals with the rs8176746 TT genotype presented low systolic blood pressure, whereas those with the rs8176740 AA genotype presented a higher HDL-C plasma concentration, as well as the lowest triglycerides concentrations among the subgroups. As far as we know, this is the first study that showed the relationship of the rs8176740 A/T with plasma lipid concentrations in individuals who were not receiving either anti-dyslipidemic or anti-hypertensive drugs; these drugs modify the plasma lipids profile, masking the real impact of ABO gene polymorphisms [26–28]. Information concerning the association between ABO blood groups and plasma lipid concentrations is still scarce. For example, Paquette et al. [7] reported that rs579459 C and rs8176746 T alleles were associated with an increase of total cholesterol, lipoprotein (a), and non-HDL-C levels with a risk of developing hypercholesterolemia. Li and Schooling [13] reported that the T allele of the rs8176746 T/G is associated with lower plasma levels of ApoB and LDL-C, but with a risk of developing some cardiovascular diseases. By the same token, Groot et al. [17] reported that rs8176746 T allele in B group individuals was associated with a lower risk of hypertension compared with O blood group. Therefore, our results and previous studies suggest a link of ABO gene polymorphisms with protection against ACS that may be partially related with HDL-C. The association of ABO groups with HDL plasma levels has been previously reported [35–37] presupposing a modification of lipoprotein metabolism but the mechanisms involved are still unknown [35]. Additional studies, such as GWAS, exome sequencing studies, and recently “exome chip” in a larger number of individuals should be undertaken.

For a correct interpretation of the impact of ABO gene polymorphisms on plasma lipid levels and blood pressure, it should be considered that control individuals were recruited based on the inclusion criteria to match some characteristics with patients. Consequently, this group does not represent a random sample of the general population [38] and the association of ABO polymorphic sites with HDL-C, triglycerides, and blood pressure were biased. Therefore, the ABO genetic impact on secondary outcomes in our study may not be

extensive to general population [38] and warrant future studies *ad hoc* to validate such findings and investigate the potential mechanisms.

Finally, we recognize that our study has some other limitations that merit to be pondered; the number of carriers of some polymorphisms and haplotypes was limited. Also, men in the ACS group were almost five times the number of women, and controls were not matched by sex and age. Considering these limitations, the effect of the SNPs on ACS incidence and some CAD risk factors should be cautiously interpreted.

Conclusions

This study demonstrated that rs579459 T/C, rs8176746 T/G, and rs8176740 A/T polymorphisms of the ABO gene and four haplotypes (H6, H7, H8, and H9) were associated with a decreased risk of ACS in Mexicans. In addition, individuals with the rs8176746 TT genotype presented low systolic blood pressure levels, whereas individuals with the rs8176740 AA genotype presented high HDL-C concentrations and a low triglycerides concentration.

Acknowledgments

The authors are grateful to Instituto Nacional de Cardiología Ignacio Chávez for the open-access funding for this article and to Silvestre Ramirez Fuentes for their participation in the collection of samples and DNA extraction. Furthermore, we are grateful to the CORE-Lab personnel of the Instituto Nacional de Cardiología Ignacio Chávez for their technical assistance.

Conflicts of interest: Authors declare no conflicts of interest.

Funding: This study was funded by the Instituto Nacional de Cardiología Ignacio Chávez, Mexico City, México (Project-22-1288).

Data availability: The data shown in this work are available upon request from the corresponding author.

Submitted: 02 May 2023

Accepted: 10 June 2023

Published online: 19 June 2023

References

- [1] Virmani R, Kolodgie FD, Burke AP, Finn AV, Gold HK, Tulenko TN, et al. Atherosclerotic plaque progression and vulnerability to rupture: angiogenesis as a source of intraplaque hemorrhage. *Thromb Vasc Biol* 2005;25:2054–61. <https://doi.org/10.1161/01.ATV.0000178991.71605.18>.
- [2] Achar SA, Kundu S, Norcross WA. Diagnosis of acute coronary syndrome. *Am Fam Physician* 2005;72:119–26. PMC16035692
- [3] Cabezas MC, Burggraaf B, Klop B. Dyslipidemias in clinical practice. *Clin Chim Acta* 2018;487:117–25. <https://doi.org/10.1016/j.cca.2018.09.010>.
- [4] Hoogeveen RC, Gaubatz JW, Sun W, Dodge RC, Crosby JR, Jiang J, et al. Small dense low-density lipoprotein-cholesterol concentrations predict risk for coronary heart disease: the atherosclerosis risk in communities (ARIC) study. *Arterioscler Thromb Vasc Biol* 2014;34:1069–1077. <https://doi.org/10.1161/ATVBAHA.114.303284>.
- [5] Christoffersen M, Tybjaerg-Hansen A. Novel genes in LDL metabolism a comprehensive overview. *Curr Opin Lipidol* 2015;26:179–87. <https://doi.org/10.1097/MOL.0000000000000175>.

- [6] Chen Y, Chen C, Ke X, Xiong L, Shi Y, Li J, et al. Analysis of circulating cholesterol levels as a mediator of an association between ABO blood group and coronary heart disease. *Circ Cardiovasc Genet* 2014;1:43–8. <https://doi.org/10.1161/CIRCGENETICS.113.000299>.
- [7] Paquette M, Dufour R, Baass A. ABO blood group is a cardiovascular risk factor in patients with familial hypercholesterolemia. *J Clin Lipidol* 2018;12:383–9. <https://doi.org/10.1016/j.jacl.2017.12.001>.
- [8] Christiansen MK, Larsen SB, Nyegaard M, Neergaard-Petersen S, Wurtz M, Grove EL, et al. The ABO locus is associated with increased platelet aggregation in patients with stable coronary artery disease. *Int J Cardiol* 2019;286:152–8. <https://doi.org/10.1016/j.ijcard.2019.01.090>.
- [9] Larson NB, Bell EJ, Decker PA, Pike M, Wassel CL, Tsia MY, et al. ABO blood group associations with markers of endothelial dysfunction in the multi-ethnic study of atherosclerosis. *Atherosclerosis* 2016;251:422–429. <https://doi.org/10.1016/j.atherosclerosis.2016.05.049>.
- [10] Paterson AD, Lopes-Virella MF, Waggott D, Borigth AP, Hosseini SM, Carter RE, et al. Genome-wide association identifies the ABO blood group as a major locus associated with serum levels of soluble E-selectin. *Arterioscler Thromb Vasc Biol* 2009;29:1958–67. <https://doi.org/10.1161/ATVBAHA.109.192971>.
- [11] Zhao C, Zhu P, Shen Q, Jin L. Prospective association of a genetic risk score with major adverse cardiovascular events in patients with coronary artery disease. *Medicine* 2017;96:51 (e9473). <https://doi.org/10.1097/MD.00000000000009473>.
- [12] Zhang H, Mooney CJ, Reilly MP. ABO blood groups and cardiovascular diseases. *Int J Vasc Med* 2012;2012:641917. <https://doi.org/10.1155/2012/641917>.
- [13] Li S, Schooling CM. A phenome-wide association study of ABO blood groups. *BMC Med* 2020;18:334. <https://doi.org/10.1186/s12916-020-01795-4>.
- [14] Gao M, Tang H, Zheng X, Zhou F, Lu W. Association analysis of GWAS and candidate gene loci in a Chinese population with coronary heart disease. *Int J Clin Exp Med* 2015;8:7497–506. PMC4509238.
- [15] Winther-Larsen A, Christiansen MK, Larsen SB, Nyegaard M, Neergaard-Petersen S, Ajjan RA, et al. The ABO locus is associated with increased fibrin network formation in patients with stable coronary artery disease. *Thromb Haemost* 2020;120:1248–56. <https://doi.org/10.1055/s-0040-1713753>.
- [16] Wauters E, Carruthers KF, Buyschaert I, Dunbar DR, Peuteman G, Belmans A, et al. Influence of 23 coronary artery disease variants on recurrent myocardial infarction or cardiac death: the GRACE genetics study. *Eur Heart J* 2013;34:993–1001. <https://doi.org/10.1093/eurheartj/ehs389>.
- [17] Groot HE, Villegas Sierra LE, Said MA, Lipsic E, Karper JC, van der Harst P. Genetically determined ABO blood group and its associations with health and disease. *Arterioscler Thromb Vasc Biol* 2020;40:830–8. <https://doi.org/10.1161/ATVBAHA.119.313658>.
- [18] Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, et al. 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J* 2020;41:407–77. <https://doi.org/10.1093/eurheartj/ehz425>.
- [19] Winther S, Schmidt SE, Rasmussen LD, Juarez Orozco LE, Stefensen FH, Batker HE, et al. Validation of the European Society of Cardiology pre-test probability model for obstructive coronary artery disease. *Eur Heart J* 2021;42:1401–11. <https://doi.org/10.1093/eurheartj/ehaa755>.
- [20] Posadas-Sanchez R, Perez-Hernandez N, Angeles-Martinez J, Lopez-Bautista F, Villareal-Molina T, Rodriguez-Perez JM, et al. Interleukin 35 polymorphisms are associated with decreased risk of premature coronary artery disease, metabolic parameters, and IL-35 levels: the genetics of atherosclerotic disease (GEA) study. *Mediators Inflamm* 2017;2017:6012795. <https://doi.org/10.1155/2017/6012795>.
- [21] DeLong DM, DeLong ER, Wood PD, Lippel K, Rifkin BM. A comparison of methods for the estimation of plasma low- and very low-density lipoprotein cholesterol. the lipid research clinics prevalence study. *JAMA* 1986;256:2372–7. <https://doi.org/10.1001/jama.1986.03380170088024>.
- [22] Lahiri DK, Nurnberger Jr. JI. A rapid non-enzymatic method for the preparation of HMW DNA from blood for RFLP studies. *Nucleic Acids Res* 1991;19:5444. <https://doi.org/10.1093/nar/19.19.5444>.
- [23] Schaid DJ. Disease-marker association. In: Elston RC, Olson JM, Palmer L, editors. *Biostatistical genetics and genetic epidemiology*. Chichester (GB): Wiley; 2002. p. 216–7.

- [24] Clayton D, Population association. In: Balding DJ, Bishop M, Cannings C, editors. Handbook of statistical genetics. Chichester (GB): Wiley; 2001. p. 519-40.
- [25] Barrett JC, Fry B, Maller J, Daly MJ. Haploview: analysis and visualization of LD and haplotype maps. *Bioinformatics* 2005;21:263-5. <https://doi.org/10.1093/bioinformatics/bth457>.
- [26] Perez-Calahorra S, Laclaustra M, Marco-Benedi V, Pinto X, Sanchez-Hernandez RM, Plana N, et al. Comparative efficacy between atorvastatin and rosuvastatin in the prevention of cardiovascular disease recurrence. *Lipids Health Dis* 2019;18:216. <https://doi.org/10.1186/s12944-019-1153-x>.
- [27] Kim KJ, Yoon J, Won KH, Lim SW, Chae IH, Lee SY, et al. Assessment of the efficacy of lowering LDL cholesterol with rosuvastatin 10 mg in four Korean statin benefit groups as per ACC/AHA guidelines (NewStar4G). *J Clin Med* 2020;9:916. <https://doi.org/10.3390/jcm9040916>.
- [28] Agabiti Rosei E, Morelli P, Rizzoni D. Effects of nifedipine GITS 20 mg or enalapril 20 mg on blood pressure and inflammatory markers in patients with mild-moderate hypertension. *Blood Press Suppl* 2005;1:14-22. <https://doi.org/10.1080/08037050510034257>.
- [29] Yang H, Wu J, Huang X, Zhou Y, Zhang Y, Liu M, et al. ABO genotype alters the gut microbiota by regulating GalNAc levels in pigs. *Nature* 2022;606:358-67. <https://doi.org/10.1038/s41586-022-04769-z>.
- [30] Qin Y, Havulinna AS, Liu Y, Jousilahti P, Ritchie SC, Tokolyi A, et al. Combined effects of host genetics and diet on human gut microbiota and incident disease in a single population cohort. *Nat Genet* 2022;54:134-42. <https://doi.org/10.1038/s41588-021-00991-z>.
- [31] Arnolds KL, Martin CG, Lozupone CA. Blood type and the microbiome—untangling a complex relationship with lessons from pathogens. *Curr. Opin. Microbiol* 2020;56:59-66. <https://doi.org/10.1016/j.mib.2020.06.008>.
- [32] Wu H, Crost EH, Owen CD, van Bakel W, Martínez Gascueña A, Latousakis D, et al. The human gut symbiont *Ruminococcus gnavus* shows specificity to blood group A antigen during mucin glycan foraging: Implication for niche colonisation in the gastrointestinal tract. *PLoS Biol* 2021;19:e3001498. <https://doi.org/10.1371/journal.pbio.3001498>.
- [33] Liu H, Zhuang J, Tang P, Li J, Xiong X, Deng H. The role of the gut microbiota in coronary heart disease. *Curr Atheroscler Rep* 2020 Oct;22(12):77. <https://doi.org/10.1007/s11883-020-00892-2>.
- [34] O'Donghaile D, Jenkins PV, McGrath RT, Preston L, Field SP, Ward SE, et al. Expresser phenotype determines ABO(H) blood group antigen loading on platelets and von Willebrand factor. *Sci Rep* 2020;10:18366. <https://doi.org/10.1038/s41598-020-75462-2>.
- [35] Di Cesare F, Tenori L, Luchinat C, Saccenti E. Association of plasma metabolites and lipoproteins with Rh and ABO blood systems in healthy subjects. *J Proteome Res* 2022;21:2655-63. <https://doi.org/10.1021/acs.jproteome.2c00375>.
- [36] Franchini M, Mengoli C, Capuzzo E, Terenziani I, Bonfanti C, Lippi G. Correlation between ABO blood group, and conventional hematological and metabolic parameters in blood donors. *Semin Thromb Hemost* 2016;42:75-86. <https://doi.org/10.1055/s-0035-1564843>.
- [37] Chen Y, Chen C, Ke X, Xiong L, Shi Y, Li J, et al. Analysis of circulating cholesterol levels as a mediator of an association between ABO blood group and coronary heart disease. *Circ Cardiovasc Genet* 2014;7:43-8. <https://doi.org/10.1161/CIRCGENETICS.113.000299>.
- [38] Schifano ED. A review of analysis methods for secondary outcomes in case-control studies. *CSAM* 2019;26:103-29. <https://doi.org/10.29220/CSAM.2019.26.2.103>.

Related articles published in BJBMS

1. Vitamin D status, serum lipid concentrations, and vitamin D receptor (VDR) gene polymorphisms in Familial Mediterranean fever

Turan Turhan et al., *Biomol Biomed*, 2018

Supplemental Data

Table S1. Allele and genotype frequencies of ABO gene polymorphisms in ACS patients and healthy controls

Polymorphic site (rsID-number)	ACS, n = 611 (n[%])	Controls, n = 676 (n[%])	*P
rs651007 T/C			
<i>Allele</i>			
C	1028 (84.5)	1153 (85.2)	NS
T	188 (15.4)	199 (14.7)	
<i>Genotype</i>			
CC	435 (71.5)	488 (72.1)	NS
CT	158 (25.9)	177 (26.1)	
TT	15 (2.4)	11 (1.6)	
rs579459 C/T			
<i>Allele</i>			
T	1032 (84.4)	1090 (80.7)	0.013
C	190 (15.5)	260 (19.2)	
<i>Genotype</i>			
TT	438 (71.6)	445 (65.9)	0.026
TC	156 (25.5)	200 (29.6)	
CC	17 (2.8)	30 (4.4)	
rs495828 T/G			
<i>Allele</i>			
G	1036 (84.7)	1153 (85.2)	NS
T	186 (15.2)	199 (14.7)	
<i>Genotype</i>			
GG	441 (72.1)	487 (72.0)	NS
GT	154 (25.2)	179 (26.4)	
TT	16 (2.6)	10 (1.5)	
rs8176746 T/G			
<i>Allele</i>			
G	1149 (94.0)	1222 (90.3)	0.0006
T	73 (5.9)	130 (9.6)	
<i>Genotype</i>			
GG	540 (88.4)	555 (82.1)	0.001
GT	69 (11.3)	112 (16.5)	
TT	2 (0.3)	9 (1.3)	
rs8176740 A/T			
<i>Allele</i>			
A	566 (46.3)	684 (50.6)	0.013
T	656 (53.7)	666 (49.3)	
<i>Genotype</i>			
AA	135 (22.0)	176 (26.0)	0.048
AT	296 (48.4)	332 (49.1)	
TT	180 (29.4)	167 (24.5)	
rs512770 T/C			
<i>Allele</i>			
C	602 (49.2)	650 (48.1)	NS
T	620 (50.7)	702 (51.9)	
<i>Genotype</i>			
CC	157 (25.6)	157 (23.2)	NS
CT	288 (47.1)	336 (49.7)	
TT	166 (27.1)	183 (27.0)	

Data are shown as n and frequency. *Chi-square test; NS: Not significant; ACS: Acute coronary syndrome.

Table S2. Association of the ABO polymorphisms with ACS in accordance to the inheritance models without adjusted by cardiovascular risk factors

Polymorphic site (rsID-number)	Model	Genotype	ACS patients, n = 611 (n[%])	Controls, n = 676 (n[%])	OR (95%CI)	P-value
rs8176746	Co-dominant	GG	540 (0.884)	555 (0.821)	0.23 (0.05–1.06)	0.0024
		GT	69 (0.113)	112 (0.166)		
		TT	2 (0.003)	9 (0.013)		
	Dominant	GG	540 (0.884)	555 (0.821)	0.60 (0.44–0.83)	0.0015
		GT + TT	71 (0.116)	121 (0.179)		
	Recessive	GG + GT	609 (0.997)	667 (0.987)	0.24 (0.05–1.13)	0.041
		TT	2 (0.003)	9 (0.013)		
	Over-dominant	GG + TT	542 (0.887)	564 (0.834)	0.64 (0.46–0.88)	0.0063
		GT	69 (0.113)	112 (0.166)		
	Additive	-	-	-	0.61 (0.45–0.81)	0.0007
rs81746740	Co-dominant	TT	180 (0.294)	167 (0.247)	0.71 (0.52–0.97)	0.045
		TA	296 (0.484)	332 (0.492)		
		AA	135 (0.221)	176 (0.261)		
	Dominant	TT	180 (0.295)	167 (0.247)	0.79 (0.62–1.01)	0.028
		TA + AA	431 (0.705)	508 (0.753)		
	Recessive	TT + TA	476 (0.779)	499 (0.739)	0.80 (0.62–1.04)	0.048
		AA	135 (0.221)	176 (0.261)		
	Over-dominant	TT + AA	315 (0.515)	343 (0.508)	0.97 (0.62–1.04)	0.789
		TA	296 (0.485)	332 (0.492)		
	Additive	-	-	-	0.84 (0.72–0.98)	0.029
rs579459	Co-dominant	TT	438 (0.717)	445 (0.659)	0.54 (0.29–1.01)	0.041
		TC	157 (0.257)	200 (0.296)		
		CC	16 (0.026)	30 (0.044)		
	Dominant	TT	438 (0.717)	445 (0.659)	0.76 (0.60–0.97)	0.026
		TC + CC	173 (0.283)	230 (0.341)		
	Recessive	TT + TC	595 (0.974)	645 (0.956)	0.58 (0.31–1.07)	0.076
		CC	16 (0.026)	30 (0.044)		
	Over-dominant	TT + CC	454 (0.743)	475 (0.704)	0.82 (0.64–1.05)	0.059
		TC	157 (0.257)	200 (0.296)		
	Additive	-	-	-	0.77 (0.63–0.95)	0.013

Bold: $P < 0.05$; ACS: Acute coronary syndrome; OR: Odds ratio; CI: Confidence interval.