Influence of Genetic Combinations on HDL-C Levels in a Southern Brazilian Population

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Abstract

Background: Low HDL-C levels are important predictors of coronary disease, the first cause of death worldwide. Many factors affect HDL-C levels, such as polymorphisms of genes encoding for key proteins of the reverse cholesterol transport pathway.

Objective: To investigate the influence of seven polymorphisms of the CETP, APOA1, ABCA1 and SCARB1 genes on HDL-C levels in a southern Brazilian population.

Methods: The polymorphisms were investigated in a sample of 500 individuals of European descent, but HDL-C levels from only 360 individuals were adjusted for cofactors using multiple linear regressions in the association study. The sample was divided in tertiles according to adjusted HDL-C levels, and allele and haplotype frequencies were compared between the 1st and 3rd tertiles of adjusted HDL-C levels.

Results: When combinations of risk alleles were tested, the frequency of allele combinations in three genes (haplotype 1 of APOA1 gene, variant 2S of SCARB1 gene, and allele B1 of CETP gene) was significantly higher in the lower tertile of adjusted HDL-C (28.3%) than in the upper tertile (14.9%; p=0.008), which indicated that the presence of these variants increased 2.26 times the chances of having HDL-C levels below 39.8 mg/dl.

Conclusion: These markers, when studied separately, are expected to have a small influence on the characteristic under analysis, but greater influence was detected when the markers were studied in combination. In a population of southern Brazilians, our data showed a significant influence of variant combinations of APOA1, SCARB1 and CETP genes on HDL-c levels. (Arq Bras Cardiol 2010; 95(4): 430-435)

Key words: Cholesterol, HDL/genetics; population/genetics; polymorphism, genetic; south region/Brazil.

Introduction

Epidemiologic studies have provided strong evidence that low concentrations of HDL cholesterol (HDL-C) are associated with increased risk of coronary artery disease (CAD)[1]. Therefore, the causes of low HDL-C levels have been intensively investigated, and genetic studies have focused on genes encoding for proteins that play important roles in the metabolism of HDL-C or in reverse cholesterol transport (RCT). Proteins in these groups include: apolipoproteins, such as A-I, A-II and E; enzymes, such as CETP, LCAT and LIPC; and membrane receptors, such as ABCA1 and SCARB1. When associated, these candidate genes are substantially polymorphic, and many studies have investigated the association of these polymorphisms with the risk of changes in lipid profiles. However, it remains unclear how these polymorphisms affect lipid profiles and whether this influence is found in different populations; this has not been studied in any South American population to this date. This study investigated the influence of seven polymorphisms of the CETP, APOA1, ABCA1 and SCARB1 genes on HDL-C levels in a southern Brazilian population.

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Methods

Subjects

The population sample consisted of 500 individuals of European descent, as previously described[2]. The volunteers included in this sample were enrolled at two clinical centers of the *Universidade Federal do Rio Grande do Sul* among individuals referred from several city health centers for routine blood tests. A questionnaire was used to collect data on drug intake and lifestyle variables, such as smoking, physical activity, alcohol consumption, oral contraceptive use, menopause, and anthropometric measurements. Smoking status was classified as non-smoker or current smoker; ex-smokers were excluded.

All individuals gave their informed consent before inclusion in the study. Exclusion criteria were: pregnancy; secondary hyperlipidemia due to kidney, liver or thyroid disease; and diabetes or fasting blood glucose levels higher than 7 mmol/l[3]. Women on hormone replacement therapy and individuals taking lipid-lowering medications, beta-blockers or anti-inflammatory drugs were also excluded.

Participants were examined in the morning after a 12-hour fast. Weight was measured in subjects without shoes and with light clothing. Body height was measured without shoes, with heels placed together and the back to the wall. Body mass index (BMI) was calculated as weight/height^2 (kg/m^2). Waist circumference was measured at the smallest horizontal circumference between the 12th rib and the iliac crest.

Laboratory analyses

Blood samples were collected after a 12-hour fast. Total cholesterol, HDL cholesterol and triglycerides were measured at each Clinical Center using standard enzymatic methods[4]. LDL cholesterol levels were calculated using Friedwald's formula[5]. Glucose levels were also measured to ensure that no individuals with diabetes were included in the study. A salting-out procedure was used to extract DNA from blood samples[6]. DNA was amplified using PCR and oligonucleotide primers under the conditions previously described for CETP[7], APOA1[8], ABCA1[9], and SCARB1[10]. The amplification products were subsequently digested with the following restriction enzymes under conditions recommended by the manufacturer: *Taq* I (CETP - TaqIB), *Msp* I (APOA1 - g-75a and c+83t), *Xag* I (ABCA1 - Arg219Lys), *Alu* I (SCARB1 - Gly2Ser), *Apa*I (SCARB1 - c780t) and *Hae* III (SCARB1 - c1050t). Genotypes were determined after electrophoresis on agarose gels containing ethidium bromide, and a 100 bp ladder was used to score the band sizes.

Statistical analyses

Allele frequencies were estimated by gene counting. A c^2 test for goodness of fit was used to check whether allele frequencies agreed with those expected according to Hardy-Weinberg equilibrium. Maximum-likelihood haplotype frequencies and linkage disequilibrium were estimated using the Arlequin 2000 software package[11]. SCARB1 and APOA1 gene haplotypes were determined using the method described by Long[12].

Only 360 subjects were analyzed in the association study between SNPs and HDL-C levels because the full sets of data for the other individuals were not available. Multiple linear regressions were performed to adjust HDL-C levels using the backward stepwise method. Covariates entered in the first model were gender, age, waist, smoking, alcohol consumption, BMI, triglyceride levels and menopause, as well as all possible interaction terms. In the final model used for HDL-C adjustment, significant covariates that remained in the model were gender, age, BMI, triglyceride levels, triglyceride levels x age, post-menopausal status and triglyceride levels x menopause for women. Triglyceride levels were log-transformed to remove skewness. The sample was divided according to HDL-C tertiles, and heterogeneity between groups in contingency tables was tested using the c^2 or the Fisher exact test. Logistic regressions were performed to obtain the odds ratio for each genetic variant or combination of variants. All analyses were made with the Statistical Package for the Social Sciences (SPSS) 11.0 for Windows.

Results

Table 1 shows the allele and genotype frequencies for the *CETP, ABCA1* and *SCARB1* genes, as well as the haplotype frequencies for the *APOA1* gene. The haplotype frequencies of the *SCARB1* gene are not shown because they did not influence HDL-C levels in any posterior analysis. All genotype frequencies are in Hardy-Weinberg equilibrium (data not shown). Strong linkage disequilibrium between the two variants of the *APOA1* gene was detected (D´= -0.84, c^2=10.04, p<0.001), and haplotype 1 *(-75g/+83c)* was the most common. For the *SCARB1* gene, allele *780t* was the most frequently found with *1050c*, which indicated a significant disequilibrium (D´= - 0.44, c^2=5.97, p=0.015). *Gly2Ser* was not linked to any of the other two variants investigated in this gene.

The prevalence of each haplotype of the *APOA1* gene and the allele frequencies of the other variants under study were compared between the 1st and 3rd HDL-C tertiles adjusted for non-genetic variables (Table 2), and the clinical characteristics according to these groups are shown in Table 3. Although the difference was not statistically significant, haplotype 1 of the *APOA1* gene, the TaqIB*1 allele of the *CETP* gene, and the *2Ser* allele of the *SCARB1* gene were more frequent in the 1st tertile (p=0.18, p=0.16 and p=0.29). When allele and haplotype frequencies were again compared between the first and the fourth HDL-C quartiles, the same trends were found, except for the *Gly2Ser* SNP of the *SCARB1* gene, that had a smaller p value (p=0.14).

Based on these results, risk alleles for low HDL-C levels were selected from the statistical comparisons that yielded values of p lower than 0.25. These variants, labeled "risk variants", are shown in Table 4, which also shows how the carriers of these variants were analyzed later: whether as homozygous, or as heterozygous and homozygous carriers.

The frequency of individuals with genetic risk combinations for low HDL-C levels was compared between the 1st and 3rd HDL-C tertiles (Table 5). First, the carriers of combinations of two deleterious variants were evaluated, as shown in Table 4, and then the frequency of carriers of combinations of three deleterious variants was compared. These comparisons showed that being a carrier of risk variants of the APOA1 and CETP genes increased 2.4 times the chance of having HDL-C levels below 39.8 mg/dl (p=0.005). When in addition to this combination the participant also carried the risk allele of the SCARB1 gene, this chance was 2.26 times greater (p=0.008). Although this gene did not seem to change the risk of having low HDL-C levels, this may be a result of the fact that only a small number of carriers had this triple combination. When SCARB1 was analyzed in combinations with CETP and APOA1, borderline results were found (OR=1.6, p=0.08), which was not observed when the CETP and APOA1 genes were evaluated separately (Table 2).

Table 1 - Allele, haplotype and genotype frequencies in the total sample

Genotype, allele, haplotype	GenBank number	Total sample, n = 500	
		n	%
***CETP*-TaqIB**	rs 708272		
B1B1		89	17.9
B1B2		241	48.4
B2B2		168	33.7
B2			35.7
ABCA1 - Arg219Lys	**rs 2230806**		
Arg Arg		219	43.8
Arg Lys		236	47.2
Lys Lys		45	9
Lys			32.6
APOA1 -g75a	**rs 670**		
gg		296	59.3
ga		176	35.3
aa		27	5.4
a			23.0
APOA1 +c83t	**rs5069**		
cc		444	89.0
ct		53	10.6
tt		2	0.4
t			5.7
APOA1 -g75a / +c83t	**rs 670 / rs5069**		
11		253	50.8
12		164	32.9
13		39	7.8
22		27	5.4
23		13	2.6
33		2	0.4
1) -75g / +83 c			71.2
2) -75a / +83 c			23.2
3) -75g / +83 t			5.6
SCARB1 - Gly2Ser	**rs 4238001**		
Gly Gly		376	75.2
Gly Ser		116	23.2
Ser Ser		8	1.6
Ser			13.2
SCARB1 - c780t	**rs 7967975**		
cc		420	84
ct		75	15
tt		5	1
T			17
SCARB1 - c1050t	**rs 5888**		
cc		180	37.2
ct		233	48.1
tt		71	14.7
t			29.3

Table 2 - Allele frequencies according to HDL-C tertiles*

	1st tertile (< 39.8 mg/dl)	3rd tertile (> 47.1 mg/dl)	p
	n = 120	n = 121	
CETP TaqIB*2 (-)	37.8	44.2	0.16
APOA1*haplotype 1	76.5	71.1	0.18†
ABCA1*219Lys	37.1	33.9	0.51
SCARB1*2Ser	15.4	12	0.29‡
SCARB1*780t	10	7.9	0.43
SRB1*1050t	37.7	38	1

** HDL levels were adjusted for gender, age, BMI, triglyceride levels, triglyceride levels x age, postmenopausal status and triglyceride levels x menopause for women; † comparison of haplotype 1 vs. other haplotypes. ‡ when differences between quartiles were tested, p value of this SNP was 0.14.*

Table 3 - Clinical and laboratory characteristics of study participants according to HDL tertiles

	1st tertile (< 39.8 mmol/l)	3rd tertile (> 47.1 mmol/l)	p
	n = 120	n = 121	
TC (mg/dl)	190.8 ± 39.8	204.1 ± 41.6	0.01
HDL-C (mg/dl)	34.8 ± 5.7	56.4 ± 9.4	<0.001
LDL-C (mg/dl)	129.9 ± 36.4	124.0 ± 38.5	0.18
Triglycerides (mg/dl)	130.6 ± 61.7	118.4 ± 68.2	0.04
BMI (kg/m^2)	25.9 ± 4.8	26.1 ± 5.3	0.78
Age (years)	42.5 ± 14.4	41.0 ± 16.3	0.45
Waist circumference (cm)	92.0 ± 12.7	89.5 ± 13.8	0.14
Gender (% men)	72.5%	38%	<0.001
Menopause[a]	15.2%	24%	0.44
Physical inactivity	62.5%	60%	0.79
Smoking[b]	34.2%	29.8%	0.49
Alcohol consumption[c]	24.2%	22.3%	0.76
Wine consumption[c]	9.2%	5.8%	0.34

[a] women on hormone replacement therapy were excluded; [b] ex-smokers were excluded; [c] alcohol or wine consumption was defined as at least one glass per week.

Table 4 - Risk variants for each gene and carrier state

Gene	Polymorphism	Risk variants	Carrier state
APOA1	*-g75a / +c83t*	Haplotype *1*	Homozygotes *11*
SCARB1	Gly2Ser	Ser	SerSer + GlySer
CETP	TaqIB	B1	B1B1 + B1B2

Discussion

Allele frequencies found in this study are mostly similar to those detected in studies with different populations.

Table 5 - Frequency of double and triple carrier-state variants of polymorphisms according to HDL-C tertiles

	OR (95%CI)	1st tertile	3rd tertile	p
Double carrier-state variants in genes		n=120	n= 121	
APOA1, CETP	2.4 (1.26 - 4.48)	85	70	0.005
APOA1, SCARB1	1.6 (0.88 - 2.91)	28	19.8	0.08
CETP, SCARB1	1.6 (0.88 - 2.91)	26	20	0.08
Triple carrier-state variants in genes				
APOA1, CETP, SCARB1	2.26 (1.19 - 4.29)	28.3	14.9	0.008

For the CETP gene, the prevalence of 35.7% for the rare allele is slightly lower than that detected in populations of exclusive European descent, which was about 40%[13-17]. In the ABCA1 gene, the values found for the Arg219Lys SNP were within the range of variation found in other populations of European descent: from 25% for Germans to 38.5% for North Americans[9,18-21]. Similar results were found for the APOA1 gene when compared with values from other populations of European descent[22]. Our data on the SCARB1 gene are comparable with those reported in the few studies published to this date, but the 17% allele frequency found in our study for intron 5 SNP and the 29.3% for the exon 8 variant are slightly different from the frequencies found by Richard et al[23] for North Americans (9% and 49%) and by Acton et al[10] for a Spanish population (10.5% and 43.8%). Our analysis of the exon 1 variant showed that the frequency of our rare allele was slightly lower than that found in a Spanish population[10]. These differences may reflect differences in the ethnic composition of the populations under comparison.

The pattern of linkage disequilibrium between the variants of the APOA1 gene was similar to those found in the literature[24]. In our population, no linkage disequilibrium was found between exon 1 SNP of the SCARB1 gene and the other SNPs under study according to findings reported for other populations[10,25,26]. However, the pattern of linkage disequilibrium between the intron 5 and exon 8 SNPs differ depending on the population under study: in Spanish[10] and North American[25] populations, the intron 5 rare variant was linked to the exon 8 common variant, which was the same that was found in our population. However, in an Austrian sample and in a different population sample in the United States, the two common alleles were linked[23,26].

When evaluated separately, our data did not show any significant influence of the polymorphisms under study on HDL-C levels (Table 4). Three of the variants under study had allele frequencies that were very similar in the comparison between the 1st and 3rd tertiles. Two of them are SCARB1 gene polymorphisms, found at intron 5 and exon 8, and the scarce data about them in the literature have not demonstrated their influence on HDL-C levels[10,25-28] nor indicated any associations with sex and use of hormones[23,28,29]. Moreover, no influence of the Arg219Lys variant on the ABCA1 gene was found in several studies with different populations[20,21,30].

We selected polymorphisms of the genes CETP, APOA1 and SCARB1 for a combined evaluation. Although some authors detected isolated effects of these genes on HDL-C levels, several other studies found that the influence of these genes is too weak to be detected when they are evaluated separately[13,26,31,32].

These differences in the magnitude of a genetic influence may reflect differences between the genetic composition of each population, as well as environmental differences between them. The evaluation of combined gene effects on HDL-C levels is rare in the literature, which makes comparison of data difficult. The evaluation of two or three risk variants revealed a significant influence of variants of the APOA1, CETP and SCARB1 genes on HDL-C levels. This finding is in agreement with studies of APOA1 and CETP genes in other populations[8,33-37]. However, for the Gly2Ser SNP of the SCARB1 gene, the few studies conducted so far associated the presence of the 2Gly allele with a decrease in HDL-C levels. In our population, the combination of the 2Ser allele and variants of APOA1 and CETP genes was more frequent in the participants with lower HDL-C levels (Table 5). Two other authors[25,27] did not detect any significant influence of this allele on HDL-C levels. Therefore, the role of this polymorphism should be further investigated, and we cannot rule out the possibility that it acts as a marker of another variant not yet studied, although it is an exchange of amino acids. The confirmation of this hypothesis would explain the differences between our data and findings reported by Acton et al[10].

The physiologic roles of these three proteins are closely associated: CETP is a key enzyme in HDL metabolism[38], whereas SR-BI and apoAI act as receptor and ligand of HDL-C[39,40]. Therefore, the interaction detected may be understood when analyzed in association with HDL-C metabolism and absorption path.

This study detected genetic influences on HDL-C levels, but it had some limitations. Major problems were the small sample size for the association study and the fact that data were missing for 140 patients. Therefore, less evident genetic influences, which can only be detected when a larger sample size is used, might not have been detected. Moreover, a prospective study of the influence of allelic combinations should be conducted to confirm the clinical impact of these genes on the lipid profile of our population.

The direction of the genetic influence on HDL-C levels seems to be, in most cases, independent of genetic background or environmental variations, but the magnitude of this effect differs greatly between different populations. Any multifactorial characteristic is influenced by several loci;

therefore, analyses of interactions between genes should be conducted, even if their separate effects cannot be detected, because that may be the only way to evaluate their actual genetic role in each population.

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Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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