



APOA5 polymorphisms associated with lipid metabolism in Brazilian children and adolescents

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ABSTRACT. Single nucleotide polymorphisms in the APOA5 gene have been studied for their association with metabolic syndrome. Thus, elucidating the effect of the mechanism involved in APOA5 gene polymorphisms on lipid metabolism is of great importance. In this study we aimed to determine the allelic and genotypic frequencies of -1131T>C, Ser19Trp, and intergenic APOA4/A5 and to evaluate the association between these variants with plasma lipid levels in children and adolescents from Brazil. This study included 524 healthy children and adolescents from Mother and Child Hospital in Recife, Pernambuco, Brazil. Data were obtained on medical history, drug intake, lifestyle variables, and demography. DNA from collected samples was extracted and genotyped for the three polymorphisms. In this studied population, triglycerides and very low-density protein levels were significantly high in subjects carrying the 19WW genotype ($P < 0.001$), demonstrating the presence of this genetic risk factor in children and adolescents.

Key words: SNP; -1131T>C; Ser19Trp; APOA4/A5; Lipid metabolism

INTRODUCTION

APOA5 is a member of the APOA1/C3/A4 gene cluster. The circulating mature form of the encoded A5 apolipoprotein is associated mainly with high-density lipoprotein (HDL) and very low-density protein (VLDL) particles (Abe et al., 2009). When human DNA was screened for APOA5 polymorphisms, more than 16 variants in young adults (18-30 years) were detected (Klos et al., 2005). The commonly analyzed variants of APOA5 are -1131T >C (rs662799), c.56C>G (rs3135506; S19W), and APOA4/A5 intergenic -12238T>C (rs1263177). Several studies have explored the association of these three polymorphisms with metabolic syndrome (Mattei et al., 2009). In general, these single nucleotide polymorphisms consistently predict high plasma triglycerides (TG), cholesterol, HDL cholesterol, LDL cholesterol, and VLDL cholesterol (Lai et al., 2005; Tai and Ordovas, 2008). The presence of the -1131C allele confers increased levels of circulating triglycerides in both healthy and dyslipidemic populations (Pennacchio et al., 2001; Pennacchio et al., 2002; Ribalta et al., 2002; Talmud et al., 2002; Horinek et al., 2003). Because hypertriglyceridemia is an independent risk factor for atherogenicity and cardiovascular diseases, elucidation of the mechanism of APOA5 gene polymorphisms on lipid metabolism is of great importance. The aim of the present study was to determine the allelic and genotypic frequencies of -1131T>C, Ser19Trp, and intergenic APOA4/A5 and to evaluate the association between these variants with plasma lipid levels in children and adolescents from Brazil.

MATERIAL AND METHODS

The study included 524 healthy children and adolescents with ages ranging from 5 to 15 years (mean 8.9 ± 2.9) from Mother and Child Hospital in Recife, Pernambuco, Brazil. All children and their parents were born in Pernambuco. A questionnaire was completed during an interview with the parents that included details on medical history, drug intake, lifestyle variables (e.g., physical activity), and demographic data. Exclusion criteria were secondary hyperlipidemia due to renal, liver, or thyroid disease, diabetes, and a parental history of diabetes or coronary artery disease. The weight and height of subjects were measured in the morning after a 12-h fast. Height was measured to the nearest centimeter using a rigid stadiometer and weight was measured to the nearest 0.1 kg using a calibrated electronic scale. This study was approved by the Ethics Committee and informed consent was obtained from all participants.

DNA was extracted from the blood cells following the protocol of Lahiri and Nurnberger (1991). Genotyping was carried out using a previously reported protocol (De França et al., 2005). Data are reported as means \pm SD. A Mann-Whitney U test was performed to analyze all variables according to the genotype. Hardy-Weinberg equilibrium (HWE) was determined using a chi-square test (χ^2). A P value <0.05 was assumed as significant in all tests conducted.

RESULTS AND DISCUSSION

We analyzed allelic and genotypic frequencies of the three polymorphisms. The rare allele frequencies for the -1131T>C, S19W, and A4/A5 polymorphisms are 0.133, 0.117, and 0.463, respectively. The frequency of 0.133 for the -1131T>C is similar to that reported for other Brazilian populations (Chen et al., 2006). Genotype frequencies for the three polymorphisms were in HWE. The results of the analysis of all variables according to the genotype are presented in Table 1.

In our population, TG and VLDL levels were significantly higher in subjects carrying the 19WW genotype ($P < 0.001$). The same results were also found in other studies. Can Dermirdögen et al. (2012) correlated the APOA5 S19W polymorphism with lipid parameters in a Turkish population. Also, the same rare allele was significantly associated with increased TG levels in a Spanish Mediterranean population (Ariza et al., 2010) and in Brazilians (De Andrade et al., 2011).

The A5 apolipoprotein is associated with the synthesis and removal of triglycerides. In conclusion, we presented frequencies of the three genetic variants of APOA5 and showed that the 19WW genotype was associated with higher TG and VLDL levels, demonstrating the presence of this genetic risk factor in children and adolescents.

Table 1. Analysis of all variables according to the genotype.

	Total N (%)	Age (M ± SD) N = 524	BMI (M ± SD) N = 524	W/H (M ± SD) N = 411	TG (M ± SD) N = 524	TC (M ± SD) N = 524	HDL (M ± SD) N = 524	TC/HDL (M ± SD) N = 524	LDL (M ± SD) N = 523	VLDL (M ± SD) N = 524
A4_A5	117 (22.33)	8.98 ± 2.89	19.16 ± 4.54	0.90 ± 0.05	89.26 ± 44.19	162.12 ± 30.88	45.32 ± 9.98	3.70 ± 0.85	99.10 ± 26.11	17.90 ± 8.84
CC	251 (47.90)	9.45 ± 2.91	19.10 ± 4.77	0.90 ± 0.05	92.67 ± 47.84	161.29 ± 32.20	44.30 ± 10.88	3.80 ± 0.84	98.50 ± 26.47	18.50 ± 9.57
CT	156 (29.77)	8.97 ± 2.81	19.28 ± 4.28	0.89 ± 0.05	89.87 ± 45.16	164.26 ± 31.98	45.22 ± 10.88	3.70 ± 0.85	101.10 ± 27.17	18.00 ± 9.04
TT	368 (70.23)	8.66 ± 2.96	18.99 ± 4.77	0.90 ± 0.05	85.73 ± 39.56	159.29 ± 27.87	46.26 ± 10.57	3.60 ± 0.85	96.30 ± 23.88	17.10 ± 7.91
CC+CT	407 (77.67)	9.12 ± 2.85	19.23 ± 4.44	0.90 ± 0.05	90.76 ± 45.98	163.32 ± 32.04	44.90 ± 9.70	3.70 ± 0.85	100.20 ± 26.94	18.20 ± 9.20
TT+TC		8.85 ± 2.87	19.17 ± 4.48	0.90 ± 0.05	88.28 ± 43.09	162.36 ± 30.53	45.62 ± 9.69	3.70 ± 0.86	99.20 ± 26.04	17.70 ± 8.63
A5_S19W	417 (79.58)	8.98 ± 2.89	19.16 ± 4.54	0.90 ± 0.05	89.26 ± 44.19	162.12 ± 30.88	45.32 ± 9.98	3.70 ± 0.85	99.10 ± 26.11	17.90 ± 8.84
SS	91 (17.37)	8.99 ± 2.89	19.05 ± 4.49	0.90 ± 0.05	87.15 ± 43.26	162.47 ± 30.73	45.63 ± 10.16	3.70 ± 0.86	99.60 ± 26.18	17.40 ± 8.66
SW	16 (3.05)	9.16 ± 2.86	19.47 ± 4.77	0.90 ± 0.06	93.56 ± 43.27	158.51 ± 30.89	43.44 ± 8.81	3.70 ± 0.79	96.40 ± 25.18	18.70 ± 8.66
WW	508 (96.95)	7.63 ± 2.94	20.08 ± 4.36	0.90 ± 0.05	119.86 ± 60.91 ^a	173.44 ± 33.42	48.02 ± 10.58	3.80 ± 1.04	101.50 ± 29.96	24.00 ± 12.17 ^b
SS+SW	107 (20.42)	9.03 ± 2.88	19.13 ± 4.55	0.90 ± 0.05	88.29 ± 43.29 ^a	161.76 ± 30.77	45.23 ± 9.96	3.70 ± 0.85	99.00 ± 26.01	17.70 ± 8.66 ^b
WW+WS		8.93 ± 2.91	19.56 ± 4.69	0.90 ± 0.06	97.49 ± 46.94	160.74 ± 31.57	44.12 ± 9.19	3.70 ± 0.83	97.10 ± 25.86	19.50 ± 9.39
A5_T-	413 (78.82)	8.98 ± 2.89	19.16 ± 4.54	0.90 ± 0.05	89.26 ± 44.19	162.12 ± 30.88	45.32 ± 9.98	3.70 ± 0.85	99.10 ± 26.11	17.90 ± 8.84
1131C	83 (15.84)	9.14 ± 2.93	19.11 ± 4.40	0.89 ± 0.05	87.41 ± 40.56	161.21 ± 29.85	45.32 ± 9.94	3.70 ± 0.84	98.60 ± 25.66	17.50 ± 8.12
TT	28 (5.34)	8.12 ± 2.48	19.53 ± 4.83	0.92 ± 0.04	99.42 ± 60.69	167.49 ± 33.34	46.21 ± 10.43	3.80 ± 0.98	101.40 ± 27.59	19.90 ± 12.14
CT	496 (94.66)	9.14 ± 2.97	18.72 ± 5.65	0.89 ± 0.05	86.50 ± 34.02	159.64 ± 37.39	42.68 ± 9.02	3.80 ± 0.59	99.70 ± 28.78	17.30 ± 6.81
CC	111 (21.18)	8.97 ± 2.89	19.18 ± 4.47	0.90 ± 0.05	89.42 ± 44.72	162.26 ± 30.52	45.47 ± 10.02	3.70 ± 0.86	99.00 ± 25.98	17.90 ± 8.95
TT+TC		8.98 ± 2.89	19.18 ± 4.47	0.90 ± 0.05	89.42 ± 44.72	162.26 ± 30.52	45.47 ± 10.02	3.70 ± 0.86	99.00 ± 25.98	17.90 ± 8.95
CC+CT		8.98 ± 2.89	19.18 ± 4.47	0.90 ± 0.05	89.42 ± 44.72	162.26 ± 30.52	45.47 ± 10.02	3.70 ± 0.86	99.00 ± 25.98	17.90 ± 8.95

^a19WW versus 19SS + 19SW = $P < 0.001$. ^b19WW versus 19SS + 19SW = $P < 0.001$. M ± SD: mean ± standard deviation; BMI: body mass index; W/H: waist-to-hip ratio; TG: triglycerides; TC: total cholesterol; HDL: high-density lipoprotein cholesterol; LDL: low-density lipoprotein cholesterol; VLDL: very low-density lipoprotein cholesterol.

Conflicts of interest

The authors declare no conflict of interest.

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