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p.Q192R SNP of *PON1* seems not to be Associated with Carotid Atherosclerosis Risk Factors in an Asymptomatic and Normolipidemic Brazilian Population Sample

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Abstract

Background: Evidences suggest that paraoxonase 1 (PON1) confers important antioxidant and anti-inflammatory properties when associated with high-density lipoprotein (HDL).

Objective: To investigate the relationships between p.Q192R SNP of *PON1*, biochemical parameters and carotid atherosclerosis in an asymptomatic, normolipidemic Brazilian population sample.

Methods: We studied 584 volunteers (females n = 326, males n = 258; 19-75 years of age). Total genomic DNA was extracted and SNP was detected in the TaqMan® SNP OpenArray® genotyping platform (Applied Biosystems, Foster City, CA). Plasma lipoproteins and apolipoproteins were determined and PON1 activity was measured using paraoxon as a substrate. High-resolution β-mode ultrasonography was used to measure cIMT and the presence of carotid atherosclerotic plaques in a subgroup of individuals (n = 317).

Results: The presence of p.192Q was associated with a significant increase in PON1 activity (RR = 12.30 (11.38); RQ = 46.96 (22.35); QQ = 85.35 (24.83) μmol/min; p < 0.0001), HDL-C (RR= 45 (37); RQ = 62 (39); QQ = 69 (29) mg/dL; p < 0.001) and apo A-I (RR = 140.76 ± 36.39; RQ = 147.62 ± 36.92; QQ = 147.49 ± 36.65 mg/dL; p = 0.019). Stepwise regression analysis revealed that heterozygous and p.192Q carriers influenced by 58% PON1 activity towards paraoxon. The univariate linear regression analysis demonstrated that p.Q192R SNP was not associated with mean cIMT; as a result, in the multiple regression analysis, no variables were selected with 5% significance. In logistic regression analysis, the studied parameters were not associated with the presence of carotid plaques.

Conclusion: In low-risk individuals, the presence of the p.192Q variant of *PON1* is associated with a beneficial plasma lipid profile but not with carotid atherosclerosis. (Arq Bras Cardiol. 2015; 105(1):45-52)

Keywords: Paraoxonase-1/genetics; Polymorphism, genetic; Carotid Artery Diseases/physiopathology; Lipoproteins, HDL.

Introduction

Human paraoxonase 1 (*PON1*-OMIM 168820) is a calcium-dependent serum esterase composed of 354 amino acids, with a molecular weight of 43kDa, and coded in chromosome 7q21. It is expressed in a variety of tissues, but synthesized mainly in the liver. PON1 binds to high-density lipoprotein (HDL) through interaction of hydrophobic N-terminus with phospholipids and with apolipoprotein A-1 (apo A-1)[1] leading to HDL important antioxidant and anti-inflammatory properties[2].

Previous studies suggest that PON1 activity could influence HDL-C levels, probably because of the involvement of PON1 in the protection against HDL oxidation[3]. Furthermore, PON1 is present in small and dense HDL particles[4], indicating that there is a relationship between PON1 activity and HDL size[5].

The relationship between PON1 activity and coronary heart disease (CHD) risk in humans has been reported among various ethnic populations; thus, two meta-analyses confirm the association of a lower PON1 activity with increased CHD risk regardless of age and ethnicity[6,7].

PON1 activity is under genetic and environmental regulation and varies widely among individuals and populations[8]. The SNP rs662, found in the coding region,

leads to a substitution of glutamine (CAA) for arginine (CGA) at position 192 (p.Q192R)[9].In addition to its effects on the enzymatic activity, several studies have been carried out to elucidate the relationship of this SNP with established cardiovascular disease (CVD) in different populations. The p.192R variant frequency was increased in CVD groups of Japanese, Caucasian and Asian-Indian populations[10-12]; however, the same associations were not found in Turkish and Finnish populations[13-14].

In the Brazilian population, the p.Q192R SNP distribution varies among ethnic groups[15]; additionally, the impact of the p.192R variant on established CVD is conflicting[16-18]. Moreover, there are no studies in our population relating SNP to CVD risk in asymptomatic individuals; indeed, studies associating the polymorphism with subclinical carotid disease in healthy individuals are rare[19].

In view of the results obtained in studies in different ethnic groups, and the scarcity of studies in low-risk populations, we investigated the relationships of p.Q192R SNP of *PON1* with biochemical parameters and carotid atherosclerosis in an asymptomatic, normolipidemic Brazilian population.

Methods

Study population

This study comprised 584 individuals selected among 1536 normolipidemic and asymptomatic volunteers of both genders, aged 19 to 75 years, who had undergone free health checkups in primary health care centers between 2008 and 2012 in Campinas and Americana (São Paulo, Brazil), as previous described by Parra et al.[20]. At admission, the individuals underwent a complete clinical evaluation and answered a detailed questionnaire to provide data on family history of premature coronary artery disease (CAD), (defined as the occurrence of acute events and/or death in first-degree relatives), past and current health status, exercise and diet habits, alcohol and tobacco use, and medications. The exercise habits were evaluated through a questionnaire adapted from Baecke et al.[21], consisting of 16 questions that include three indexes of habitual physical activities in the last 12 months, defined as (*i*) occupational or labor physical activity index; (*ii*) free time physical exercise index; and (*iii*) free time and locomotion activity index. Furthermore, diet habits were evaluated by a dietary frequency questionnaire (classified as daily, weekly and monthly/no consumption) adapted from Furlan-Viebig and Pastor-Valero[22] of ten food classes as follows: (*i*) milk and dairy products; (*ii*) meat, fish and eggs; (*iii*) vegetables; (*iv*) fruits; (*v*) natural juices; (*vi*) breads, cereals and tubers; (*vii*) oils and fats; (*viii*) sweets, snacks and treats; (*ix*) non-alcoholic beverages and (*x*) preparations and miscellaneous.

Exclusion criteria included regular use of medications, especially those which interfere with the lipid metabolism, such as statins, hormonal replacement therapy and contraceptives. The medications allowed in the protocol included: (1) vitamins, nutritional supplements and homeopathy; (2) antidepressants; (3) analgesics (sporadic use); (4) antiallergics and proton pump inhibitors; and (5) two or more of the mentioned medications combined. Additionally, we excluded volunteers with thyroid dysfunction; dyslipidemia; diabetes mellitus; metabolic syndrome; obesity; pregnancy; arterial hypertension; liver, lung or kidney diseases; alcohol abuse (> 14g/day); and smoking.

Venous blood samples were drawn after a 12h fasting period for serum and EDTA plasma separation by centrifugation (4°C, 1000 x *g*, 10 minutes), and stored at -80°C until analysis. In another visit, the volunteers underwent carotid ultrasonography.

The Medical Sciences Ethics Committee of the University of Campinas approved this study and all volunteers gave written informed consent.

Biochemical analysis

Fresh serum samples were analyzed for total cholesterol, HDL-C, triglycerides and glucose in Modular Analytics® EVO (Roche Diagnostics, Burgess Hill, West Sussex, UK) using Roche Diagnostics® reagents (Mannheim, Germany). Apolipoproteins A-1 and B were determined by nephelometry in BN II (Siemens Healthcare Diagnostics, Marburg, Germany) automated system using commercially available assays (Dade-Boehringer®, Deerfield, Illinois, USA). Low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedwald formula[23], while very-low density lipoprotein cholesterol (VLDL-C) was calculated using the formula triglycerides/5[21].

C-reactive protein (CRP) was measured by immunoturbidimetry in a high-sensitivity method (hsCRP), using the commercially available assay Tina-quant CRP (Latex) HS-Roche (Roche Diagnostics®, Mannheim, Germany).

HDL particle size was determined by the dynamic light scattering (DLS) technique after chemical precipitation of apo B-containing lipoproteins in plasma samples using polyethylene glycol (PEG) 8000 (Sigma-Aldrich, St. Louis, USA)[24]. The measurements were performed in triplicate in the Nanotrac Particle Size Analyzer (Microtrac, North Largo, Florida, USA) and a 100nm polymeric nanoparticle was used as the standard; a control sample obtained from the same individual plasma was used in all determinations.

Plasma activity of cholesteryl ester transfer protein (CETP) and phospholipid transfer protein (PLTP) was determined by radiometric assays using exogenous substrates[25,26]. Additionally, PON1 activity was measured using paraoxon (diethyl-p-nitrophenylphosphate, Sigma, St. Louis, MO, USA) as substrate[27].

SNP genotyping

Total genomic DNA was extracted from peripheral mononuclear blood cells, according to the standard phenol/chloroform method. Quality, integrity and concentration were determined and DNA samples were stored at −20 °C prior to use.

Genotype analysis for p.Q192R SNP of *PON1* was performed using the OpenArray®Real-Time PCR Platform (Applied Biosystems, Foster City, CA), following the

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manufacturer's standard protocol. The genotypes were determined using the TaqMan®Genotyper Software 1.0.1. (Applied Biosystems, Foster City, CA, USA). Individuals with the GG genotype were designated as RR (p.192R homozygous), while those with the AA genotype were named QQ (p.192Q homozygous) and those with the GA genotype (heterozygous) were designated as RQ.

Carotid intima-media thickness (cIMT) measurements

All volunteers were invited to undergo carotid intima-media thickness measurements and a subgroup of 317 individuals underwent the test. Carotid ultrasonography was performed by a single trained sonographer, blind to the study subjects. High-resolution B-mode ultrasonography was carried out using a 6-9 MHz linear array ultrasound imaging system (ATL HDI 1500 and 3500 Ultrasound System, Advanced Technology Laboratories Ultrasound, Bothell, EUA) and longitudinal measurements were made of segments of the common carotid arteries at the distal wall and at 1 cm from the bifurcation. Mean cIMT was calculated based on the average of five measurements of the right and left sides and expressed in millimeters (mm); the presence of carotid plaques was also investigated.

Statistical analyses

Statistical analyses were performed using the SPSS 16.0 (SPSS Inc., USA) and R software (R Development Core Team, Vienna, Austria). Normal distribution of the variables was determined by the Kolmogorov-Smirnov test. Normal data are expressed as mean ± standard deviation, and non-normal data are expressed as median (interquartile range).

Comparisons between genotypes were performed using ANOVA or Kruskal-Wallis, followed by the Bonferroni's test for normal and non-normal data, respectively. Additionally, chi-square test was performed for categorical variables. When necessary, the comparisons were adjusted by ANCOVA for age, gender and body mass index (BMI).

Stepwise regression analyses were performed to verify the main determinants of PON1 activity, and included the variables age, gender, BMI, HDL particle size, CETP, PLTP and p.Q192R SNP of *PON1*. The RR genotype was used as a reference group.

Univariate and multiple linear regression analyses were performed to evaluate the influence of HDL-C, apo A-1, HDL particle size, hsCRP, PON1 activity and p.Q192R SNP on mean cIMT; the analyses were controlled for age, gender and BMI. In addition, logistic regression analysis determined the odds ratio (OR) for the presence of carotid plaques according to HDL-C, apo A-1, HDL particle size, hsCRP, PON1 activity and p.Q192R SNP, also controlled for age, gender and BMI. The G* Power software was used in order to evaluate whether the sample had statistical power to detect associations, according to the following parameters: OR = 1.5; significance level α = 0.008 (adjusted for multiple comparisons); two-tailed; statistical power 1-β = 80%. In this way, the sample showed 99.9% and 54.98% of statistical power for multiple linear regression and logistic regression analysis, respectively.

P-values < 0.05 (corrected by Bonferroni for multiple tests) were considered statistically significant.

Results

The study population was comprised of 56% females and 44% males, and genotype frequency was 37%, 45% and 19% for RR, RQ and QQ groups, respectively. The p.Q192R SNP was in Hardy–Weinberg equilibrium. Furthermore, all volunteers were asymptomatic; non-smokers; had no past or current history of thyroid dysfunction, dyslipidemias, diabetes mellitus or other endocrine diseases; no pregnancy, obesity, metabolic syndrome, arterial hypertension; no liver, lung or kidney diseases.

Clinical and biochemical characteristics were described and compared between genotypes, as shown in table 1. QQ volunteers presented a significant increase in PON1 activity, total cholesterol, HDL-C and apo A-1 when compared to RQ or RR groups. No significant differences were observed regarding all the other biochemical parameters, mean cIMT, presence of plaques, family history of premature CAD, alcohol consumption, medication use and physical activity indexes. Additionally, the frequencies (daily, weekly and monthly/no consumption) of the ten studied food classes were not significantly different between the genotypes, as follows: milk and dairy products (p = 0.716); meat, fish and eggs (p = 0.269); vegetables (p = 0.766); fruits (p = 0.198); natural juices (0.412); breads, cereals and tubers (0.136); oils and fats (p = 0.435); sweets, snacks and treats (p = 0.545); non-alcoholic beverages (p = 0.454) and preparations and miscellaneous (p = 0.874).

Plasma PON1 activity was influenced only by QQ (R^2 = 39%) and RQ (R^2 = 19%) genotypes, as demonstrated in table 2; thus, other non-studied factors have an influence of 42%.

Univariate linear regression analysis demonstrated that the studied parameters, including p.Q192R SNP, were not associated with mean cIMT, as demonstrated in table 3. As a result, in the multiple regression analysis no variables were selected with 5% significance. In addition, for the logistic regression analysis the studied parameters were not associated with the presence of plaques, as demonstrated in table 4.

Discussion

Studies conducted in different ethnic groups have reported diverse distribution of the p.192Q and p.192R variants. The p.192Q variant has been described as being more frequent in Caucasians[28], and p.192R, in Japanese, Chinese and Hispanic populations[29-31]. In addition, the frequencies have been previously explored in a Brazilian population sample, in which significant differences between genotypes regarding European descendants and Afro-Brazilians were demonstrated[15]. In our study, the p.192R variant represents 59% of the total sample, and p.192Q, 41%, similar to the frequencies observed in the Afro-Brazilian population[15].

Several SNPs in different regions of *PON1* have been identified, including the amino acid 192, which is one of the most frequently studied in order to identify the influence on enzyme activity and cardiovascular disease[32]. In the present study, we demonstrated that the p.192Q variant significantly modulates PON1 activity and the levels of apo A-1, cholesterol and HDL-C.

Table 1 – Descriptive and comparative analyses of clinical, anthropometrical and biochemical parameters among *PON1* p.Q192R genotypes

Parameters	RR (n = 215)	RQ (n = 260)	QQ (n = 109)	p
Gender (Female/Male)	112/103	153/107	61/48	-
Age (years)	45 (23)	44 (27)	46 (17)	-
BMI (kg/m^2)	23.6 ± 2.8	23.4 ± 2.9	24.5 ± 2.9	-
Waist circumference (cm)	78 (15)	76 (13)	74 (10)	0.413
SBP (mmHg)	120 (15)	120 (20)	120 (20)	0.334
DBP (mmHg)	80 (10)	80 (14)	80 (8)	0.260
Total cholesterol (mg/dL)	170 ± 32	174 ± 29	176 ± 30	0.044[†]
HDL-C (mg/dL)	45 (37)	62 (39)	69 (29)	< 0.001[†‡]
HDL size (nm)	7.85 (0.91)	8.00 (1.02)	8.06 (0.88)	0.467
Triglycerides (mg/dL)	77 (43)	74 (45)	64 (33)	0.054
LDL-C (mg/dL)	100 ± 26	101 ± 23	101 ± 22	0.550
VLDL-C (mg/dL)	15 (8)	15 (9)	13 (7)	0.069
Apo A-I (mg/dL)	140.76 ± 36.39	147.62 ± 36.92	147.49 ± 36.65	0.019[†]
Apo B (mg/dL)	76.37 ± 19.64	76.80 ± 17.11	75.54 ± 18.72	0.472
CETP (%)	13.55 ± 5.45	13.38 ± 5.92	13.20 ± 5.24	0.616
PLTP (nmolesFC/mL/h)	6321 (3074)	6086 (2253)	6088 (2393)	0.414
PON1 (µmol/min)	12.30 (5.90)	46.95 (22.35)	85.35 (21.18)	< 0.001[*†‡]
Glucose (mg/dL)	84 (12)	83 (10)	84 (9)	0.499
hsCRP (mg/L)	0.80 (1.00)	0.80 (1.13)	0.90 (1.65)	0.231
Mean cIMT (mm)	0.60 (0.20)	0.60 (0.30)	0.58 (0.15)	0.207
Carotid Plaques (Yes/No, %)	19/81	18/82	11/89	0.712
Family history of premature CAD (Yes/No, %)	7/30	6/39	6/15	0.659
Alcohol consumption (Moderate/No consumption, %)	7/31	9/36	3/14	0.503
Medications (Yes/No, %)	5/31	8/37	3/16	0.903
Occupational or labor physical activity index	2.75 (1.00)	2.75 (0.87)	2.87 (0.62)	0.493
Free time physical exercise index	2.00 (1.00)	2.00 (1.25)	2.00 (1.50)	0.913
Free time and locomotion activity index	2.50 (1.00)	2.50 (1.00)	2.50 (1.00)	0.998

(n): number of individuals or as shown below; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; VLDL-C: very low-density lipoprotein cholesterol; Apo: apoliprotein; hsCRP: high-sensitivity C reactive protein; CETP: cholesteryl ester transfer protein; PLTP: phospholipid transfer protein; FC: free cholesterol; PON1: paraoxonase 1; CAD: coronary artery disease; cIMT: carotid intima-media thickness: RR (119), RQ (132),QQ (66). Normal and non-normal data are presented as mean ± standard deviation and median (interquartile range), respectively. P values - ANOVA or Kruskal-Wallis, adjusted with ANCOVA for age, gender and BMI; significant differences (p ≤ 0.05) by Bonferroni's were indicated by *RR≠RQ; †RR≠QQ; ‡QQ≠RQ.

Table 2 – Stepwise regression analysis for PON1 activity in the studied population

Parameters	R^2	Cumulative R^2	F	p
QQ	0.3876	0.3876	193.7	< 0.0001
RQ	0.1918	0.5794	210.1	< 0.0001
Non-studied factors	0.4206			

R^2: coefficient of determination. Variables analyzed following the stepwise criteria are age, gender (female x male), body mass index, total cholesterol, HDL-C, HDL particle size, CETP, PLTP and p.Q192R SNP. The RR genotype was used as reference group.

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Table 3 – Univariate and multiple linear regression analysis for cIMT in the studied population

Univariate linear regression (n = 310)				
Parameters	Estimate	SE	p	R^2
p.Q192R (RR x QQ)	0.55	8.86	0.951	0.001
p.Q192R (QQ x RQ)	-17.26	10.57	0.104	0.005
HDL-C	0.04	0.21	0.845	< 0.0001
Apo A-I	0.08	0.12	0.482	< 0.0001
HDL particle size	0.92	6.96	0.895	< 0.0001
hsCRP	0.52	0.87	0.554	< 0.0001
PON1 activity	-0.08	0.14	0.548	< 0.0001
Multiple linear regression analysis (n = 310)				
Independent variable	Dependent Variable	Estimate	p	R^2
Mean cIMT	-	-	-	-

The variables were transformed into ranks due the absence of Normal distribution and the analyses were controlled for age, gender and BMI. SE: standard error; R^2: coefficient of determination; HDL-C: high-density lipoprotein cholesterol; apo: apolipoprotein; hsCRP: high sensitivity C reactive protein; PON1: paraoxonase 1; cIMT: carotid intima-media thickness

Table 4 – Logistic regression analysis for the presence of carotid atherosclerotic plaques in the studied population

Univariate logistic regression (n = 308)					
Parameters	Estimate	SE	p	OR	95%CI
p.Q192R (RR x QQ)	0.270	0.471	0.567	1.310	0.520; 3.303
p.Q192R (QQ x RQ)	0.266	0.464	0.566	1.305	0.526; 3.241
HDL-C	-0.002	0.009	0.777	0.997	0.980; 1.015
Apo A-I	0.003	0.004	0.486	1.003	0.994; 1.012
HDL particle size	-0.370	0.299	0.216	0.691	0.384; 1.241
hsCRP	-0.032	0.040	0.418	0.968	0.895; 1.047
PON1 activity	-0.005	0.005	0.334	0.994	0.983; 1.006
Multiple logistic analyses (n = 308)					**95%CI**
Independent variable	Dependent variable	Estimate	p	OR	CI95%
Carotid plaques	-	-	-	-	-

The variables were transformed into ranks due the absence of Normal distribution and the analyses were controlled for age, gender and BMI.SE: standard error; OR: odds ratio; CI: confidence interval; HDL-C: high-density lipoprotein cholesterol; apo: apolipoprotein; hsCRP: high sensitivity C reactive protein; PON1: paraoxonase 1.

Genetic variations have a major impact on PON1 catalytic activity; indeed, amino acid 192 is an important active-site of the enzyme and constitutes part of HDL surface anchoring[33]. Studies regarding the impact of p.Q192R on the hydrolytic activity demonstrated that the p.192R variant shows higher activity towards paraoxon and phenylacetate, compared to p.192Q[8]. Despite that, in this study, p.192Q was associated with increased activity towards paraoxon and the stepwise regression analysis suggests that 58% of PON1 activity was determined by this variant.

There has been evidence associating higher PON1 activity with increased HDL-C levels[3]. Indeed, Blatter Garin et al.[34] observed positive correlations between PON1 activity, HDL-C and apo A-1 levels in a population with confirmed coronary artery disease as well as in control individuals. However, the p.Q192R SNP of *PON1* was not associated with apo A-1 and HDL-C levels in any of the groups. On the other hand, our study demonstrated that the p.192Q variant is a significant predictor of increased apo A-1 and HDL-C levels in normolipidemic and asymptomatic individuals.

Low plasma PON1 activity has been positively associated with increased CVD risk regardless of age and ethnicity, as reported by numerous studies, including meta-analyses[6,7]. In this context, multiple clinical reports focused on the role of *PON1* polymorphisms that directly affect PON1 activity on CVD[35-37]. In a meta-analysis including 88 studies, Wang et al.[35] demonstrated that subjects with the p.192R variant presented a higher CVD risk than those with the p.192Q variant of *PON1*; however, other studies still show controversies regarding the role of these alleles[35]. Indeed, there was one strong association correlating the p.192R variant with ischemic stroke,

but the risk was confined to Caucasians[36]; furthermore, Birjmohun et al.[37] demonstrated that p.Q192R SNP of *PON1* did not predict the CVD risk in individuals from the EPIC-Norfolk cohort study[37].

The impact of p.Q192R SNP was also explored in Brazilian population samples. Rios et al.[16] studied both p.Q192R and p.M55L SNPs of *PON1* in 712 patients, of whom 437 were Caucasians and 275 Afro-Brazilians with established CAD (obstructive lesions higher than 50%). The p.Q192R SNP was not associated with CAD; however, only in Caucasian men did the RR genotype lead to a decrease in HDL-C levels. Oliveira et al.[17] also determined the influence of p.Q192R and p.M55L SNPs on 352 patients with angiographically defined CAD and 380 matched controls for age and gender at a high risk for CAD. Similarly, no significant associations were found between the p.Q192R SNP and CAD. In addition, Voetsh et al.[18] evaluated the association of p.Q192R and p.M55L SNPs with the risk of arterial ischemic stroke in 118 patients (with a first nonfatal stroke occurring before 45 years of age) and 118 age- and sex-matched controls. The RR genotype was more frequent in patients with ischemic stroke and was independently associated with the disease risk. In this context, the Brazilian population presents controversial relationships regarding the p.Q192R SNP and cardiovascular disease.

In addition to the reports involving the role of p.Q192R SNP of *PON1* on cardiovascular disease, previous studies conducted in disease states (mainly diabetes and/or hypercholesterolemia) showed inconsistent results regarding the associations between p.Q192R SNP and cIMT[38-40], a surrogate marker of coronary atherosclerosis[41].

Regarding the association of cIMT with p.Q192R in healthy individuals Dessi et al.[19] observed an increase, although not significant, of cIMT in the p.192R variant among genotypes. Additionally, Karvonen et al.[42] did not observe significant differences regarding cIMT in a large cohort of hypertensive and control individuals. Similarly, there is a lack of associations of p.Q192R with cIMT and carotid atherosclerotic plaques in our study, strongly suggesting that this SNP, in low-risk individuals, is not a major parameter associated with carotid atherosclerosis.

The results should be carefully interpreted since there are limitations that must be addressed, such as the relatively small sample size given the study design, especially its rigorous inclusion and exclusion criteria. In addition, the number of volunteers who underwent the carotid IMT exam was not enough to reach the minimum statistical power (80%) for the logistic regression analysis, since the predicted sample size to meet this condition was 480 individuals. Furthermore, the low compliance to a second visit for cIMT measurements limited our conclusions and the regression analysis could not provide evidences of a causal relationship between *PON1* polymorphism and carotid plaques.

Conclusion

Despite the absence of associations of p.Q192R SNP with cIMT and carotid plaques, there is evidence in our study that the p.192Q variant exerts important beneficial influences on the plasma lipid profile. However, larger studies are needed to further establish the association of p.Q192R SNP with CVD in low cardiovascular risk individuals.

Author contributions

Conception and design of the research:Scherrer DZ, Quintão ECR, Faria EC. Acquisition of data:Scherrer DZ, Zago VHS, Vieira IC, Parra ES, Panzoldo NB, Alexandre F, Baracat J. Analysis and interpretation of the data: Scherrer DZ, Zago VHS, Vieira IC, Secolin R, Baracat J, Faria EC. Statistical analysis: Scherrer DZ, Zago VHS, Secolin R. Obtaining financing: Quintão ECR, Faria EC. Writing of the manuscript:Scherrer DZ, Zago VHS, Faria EC. Critical revision of the manuscript for intellectual content: Scherrer DZ, Zago VHS, Vieira IC, Parra ES, Panzoldo NB, Alexandre F, Secolin R, Quintão ECR, Faria EC.

Potential Conflict of Interest

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

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Study Association

This study is not associated with any thesis or dissertation work.

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