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The Q192R polymorphism of the paraoxonase 1 gene is a risk factor for coronary artery disease in Saudi subjects

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Abstract Paraoxonase-1 (PON1) is a HDL-bound antioxidant enzyme that protects LDL from oxidative modification. Discovery of the antioxidant properties of PON1 led to extensive research on its role in the initiation and progression of atherosclerosis. The Q192R (rs662; A/G) polymorphism, which results in the glutamine to arginine substitution at position 192, of the PON1 gene has been linked to increased atherosclerosis risk in several but not all population studies. Besides genetic factors, environmental variables and ethnicity have been implicated as factors responsible for the ambiguity in relating the PON1 gene with atherosclerotic risk. Here, we tested the association of the Q192R polymorphism with coronary artery disease (CAD) in Saudi ethnic subjects taking environmental factors into consideration. The genomic DNA samples from 121 angiographically confirmed CAD cases and 108 normal healthy control subjects were genotyped by PCR–RFLP analysis. The distribution of QQ, QR, and RR genotypes was significantly different between cases and controls ($p < 0.005$). The RR genotype was associated with CAD risk independently of several established risk factors including age, gender, smoking, obesity, and diabetes (OR 2.2, 1.4–7.4, $p < 0.01$). Genotype-based stratification of demographic and biochemical data revealed that the RR genotype has proatherogenic properties. This study, thus, identifies the Q192R polymorphism as an additional risk factor for CAD in the Saudi population and suggests that it may have prognostic value. The negative effect of this genetic variant is presumably due to the diminished ability of the RR variant genotype of PON1 to blunt LDL oxidation.

Keywords Paraoxonase-1 gene · Q192R · Coronary artery disease · PON1 · Saudi Arabia

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Introduction

Human paraoxonase 1 (PON1) is a 44-kDa calcium-dependent glycoprotein, predominantly expressed in the liver, that circulates bound to high-density lipoprotein (HDL) particles [1, 2]. PON1 was initially identified by its capacity to hydrolyze multiple organophosphates, including paraoxon, diazoxon, sarin and soman and arylesters, such as phenylacetate [3, 4]. PON1 became the focus of intense research both at phenotypic and genetic levels subsequent to the identification of its antioxidant properties, particularly its capacity to protect LDL from oxidative damage. Oxidative modification of LDL is believed to be a major triggering event in the initiation and progression of atherosclerosis and cardiovascular events [5, 6]. Experimental evidence establishes the PON1 as an atheroprotective molecule; PON1 attenuates generation and accumulation of lipoperoxides in LDL, reduces the ability of oxidized LDL to induce monocyte binding, transmigration and inflammation in the endothelium, protects HDL from oxidation, and augments its ability to cellular cholesterol efflux [7–10]. Finally, mice

lacking the paraoxonase gene exhibit increased macrophage oxidative stress and are more susceptible to atherosclerosis [11, 12].

The enzymatic activity of PON1 is measured against the artificial substrate paraoxon. Although demographic and environmental factors exert modulating effects, the PON1 gene product is a major determinant of enzyme activity [13, 14]. PON1 gene is located in chromosome 7q21.3, along with two adjacent genes, paraoxonase 2 and paraoxonase 3, which share 65 % similarity at amino acid level [15]. Among several genetic aberrations, the Q192R (rs662) polymorphism in the coding region of PON1 gene, that results in a glutamine (Q) to arginine (R) (A/G) substitution at position 192, was widely studied and found to profoundly decrease its enzymatic activity toward paraoxon [16, 17]. Indeed, the Q192 isoform possesses lower enzymatic activity for paraoxon than the R192 isoform [16, 17]. Despite its increased affinity for paraoxon, the R192 allele is less effective in protecting LDL from oxidative modification than the Q192 allele due to reduced hydrolysis of lipid peroxides [18, 19]. Thus, the efficacies of Q and R alleles toward lipid peroxides are opposite to that toward paraoxon. PON1 activity for paraoxon has been consistently reported to be significantly diminished in atherosclerosis and other cardiovascular diseases, suggesting the possible involvement of PON1 in the pathogenesis of these disorders [20–22].

Considering the lower efficacy of R192 allele in protecting the LDL from oxidative modification, a large number of studies have assessed the relations of the Q192R polymorphism with atherosclerosis and other cardiovascular complications. A number of studies have found a significant association between R192 allele and an elevated atherosclerosis risk. For example, the Q192R polymorphism either singly or in a haplotype combination with other PON1 SNPs was found to be significantly linked to CAD risk in an Indian population [23]. In a prospective case control study with a 10-year follow-up, the R allele was found to exert increased CAD risk in Netherlanders [24]. In Japanese population, the R192 allele frequency was significantly correlated with CAD risk and this relationship remained significant even after controlling for risk factors [25, 26]. Besides, Q192R polymorphism is a risk factor for both CAD and myocardial infarction in Caucasian subjects with type-2 diabetes [27, 28]. Likewise, in Asian Indians and American population, an increased frequency of Q192R polymorphism was found in CAD patients [29, 30]. Contrastingly, the above reported relationship between Q192R polymorphism and CAD risk could not be verified by several population studies including Caucasian [31–35], Taiwanese [36], American [37], and Turkish [38]. Collectively above data imply that besides genetic variability, other factors may play a role in the CAD etiology. The demographic and environmental variables and ethnicity can all contribute to the ambiguity in relating the Q192R polymorphism with atherosclerosis. Thus, in this case–control study, we tested whether the Q192R polymorphism represents an additional risk factor for CAD and whether it can predict the disease status independently of other environmental factors in a Saudi Arabian ethnic population.

Materials and methods

Subjects

The study was conducted in accordance with the guidelines set by the Ethics Committee of Research Center, College of Science, King Saud University. All subjects recruited in this study are of native Saudi Arabians. Study includes consenting, angiographically diagnosed CAD patients ($N = 121$) with at least one major coronary artery showing $\geq$70 % of stenosis. Subjects with congestive heart failure, cardiomyopathy, congenital heart disease, hepatic, and renal disease were excluded from the study. Patients, who experienced recent acute myocardial infarction and had recent coronary angioplasty or bypass surgery, were also excluded from the study. Normal healthy subjects ($N = 108$) without CAD and any other clinical complications were defined as those who were asymptomatic, had no signs of myocardial ischemia as determined by electrocardiogram (ECG), and had negative cardiovascular disease history. Information on age, gender, socio-demographic characteristics, personal and familial medical history, smoking and the use of medications was obtained through a standard questionnaire.

Anthropometric and clinical parameters

A full physical examination of all the subjects was carried out. Anthropometric data, including weight and height, were collected using standard and well-established methods. Height and weight were recorded to the nearest 0.5 cm and 0.1 kg, respectively. The body mass index (BMI) was calculated by using the formula weight (kg)/height (m^2). Systolic and diastolic blood pressures were measured twice at an interval of 30 min using automated oscillometric device. An average value of the two readings was considered.

Biochemical measurements

Fasting blood samples were collected and the plasma was separated by Ficoll-Paque PLUS (GE Health Care, Germany) gradient centrifugation. Glucose, total cholesterol, and triglycerides were measured by standard enzymatic methods using a fully automated analyzer (Konelab, Finland). HDL-

Table 1 General characteristics of control and CAD patients

Parameters	Control ($N = 108$)	CAD ($N = 121$)	p value
Gender (M/F)	40/68	71/50	<0.005
Age (years)	41.1 ± 11.5	59.4 ± 9.9	<0.001
BMI (kg/m^2)	27.6 ± 5.0	30.9 ± 6.1	<0.001
Smoking (%)	46.2	83.7	<0.001
SBP (mmHg)	116.9 ± 15.2	137.1 ± 17.9	<0.001
DBP (mmHg)	79.5 ± 12.3	77.7 ± 10.4	0.30
Glucose (mmol/l)	5.6 ± 1.2	8.3 ± 1.5	<0.001
Insulin (μIU/ml)	6.8 ± 2.1	8.2 ± 2.2	0.76
HDL-cholesterol (mmol/l)	1.2 ± 0.27	0.86 ± 0.33	<0.001
Total cholesterol (mmol/l)	4.4 ± 0.93	5.0 ± 1.0	<0.001
LDL-cholesterol (mmol/l)	3.1 ± 0.98	3.9 ± 1.1	<0.001
Triglycerides (mmol/l)	1.4 ± 0.75	1.8 ± 0.87	<0.01

p value significant at <0.05

BMI body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *CAD* coronary artery disease

cholesterol levels were determined by phosphotungstenic acid/magnesium chloride precipitation (Konelab, Finland). Insulin was estimated enzymatically using INS-ELISA kit following the manufacturer's instructions (DIAsource Immunoassays, Nivelles, Belgium). LDL-cholesterol was calculated using the Friedewald equation.

Genotyping of Q192R polymorphism

Genotyping was carried out by PCR amplification of peripheral blood genomic DNA, extracted using blood genomic prep mini spin kit (GE Health Care, Buckinghamshire, UK), followed by restriction fragment length polymorphism analysis (RFLP). A 238 base pair genomic DNA (5 μg) was amplified using the PON1 gene-specific forward primer, 5′-GGG ACC TGA GCA CTT TTA TGG C-3′, and the reverse primer, 5′-CAT CGG GTG AAA TGT TGA TTC C-3′. PCR conditions include an initial denaturation of 95 °C for 5 min followed by 35 cycles, each consisting of denaturation (94 °C, 15 s), annealing (60 °C, 40 s), and extension (72 °C, 60 s) and a final extension at 72 °C, for 5 min. Amplified products were digested with AlwI (BspPI) restriction enzyme (New England Biolabs, UK) at 37 °C for 7 h and resolved by agarose gel electrophoresis. The QQ genotype was determined by the presence of single 238 base pair band, and the RR genotype was ascertained by the presence of 172 and 66 base pair bands, while the QR genotype was established by the presence of 238, 172, and 66 base pair bands. Genotyping errors were tackled by using the high-quality genomic DNA, reagents and carrying out repeated and blind genotyping with duplicate sample of each subject.

Statistical analysis

Data were analyzed by SPSS version 16.0. All continuous variables were represented by mean ± standard deviation. Chi-square test was used to test for the differences in frequencies between the groups and genotypes. Odds ratios (95 % CI) were computed, testing the association of genotypes and CAD using binary logistic regression, keeping wild type as the reference. Multinomial logistic regression was used to test for association of disease severity and genotypes, assessing independence from potential confounders. Variables such as age, gender, smoking status, diabetic status, BMI, SBP, Waist, FBG, HDL, total cholesterol, LDL, and triglycerides were included into the multinomial logistic model. Analysis of variance (ANOVA) was done to compare the genotype group differences for various parameters. Level of significance was given at $p \leq 0.05$.

Results

Anthropometric, clinical, and biochemical parameters

The baseline characteristics of control and CAD subjects are presented in Table 1. Compared to controls, patients had a significantly greater proportion of men ($p < 0.005$) and smokers ($p < 0.001$) and were significantly older than the control ($p < 0.001$) and had increased BMI ($p < 0.001$), systolic blood pressure ($p < 0.001$), fasting glucose ($p < 0.001$), total cholesterol ($p < 0.001$), LDL-cholesterol ($p < 0.001$), and triglycerides ($p < 0.01$). In contrast, patients had significantly decreased HDL-cholesterol levels compared to controls ($p < 0.001$). No significant differences were found in the diastolic blood pressure and circulating insulin levels.

Q192R genotype and allele distribution

We compared the genotype and allele distribution of Q192R polymorphism in CAD and control subjects to

Table 2 The distribution and odds ratios of genotypes and alleles of the Q192R polymorphism in control and CAD patients

Genotype	Control *N* (%)	CAD *N* (%)	ORs (95 % CI)	*p* value
QQ	60 (55.6)	40 (33.1)	Reference	
QR	37 (34.3)	57 (47.1)	2.3 (1.3–4.1)	<0.01
RR	11 (10.1)	24 (19.8)	3.2 (1.4–7.4)	<0.01
Allele				
Q	157 (72.7)	137 (56.6)	Reference	
R	59 (27.3)	105 (43.4)		<0.001

p value significant at <0.05

CAD coronary artery disease, *ORs* odds ratios

examine their association with CAD risk. Distribution frequencies of QQ, QR, and RR genotypes among the CAD and control subjects are provided in Table 2. The distribution of QQ, QR, and RR genotypes ($p < 0.005$) as well as Q and R alleles ($p < 0.001$) was significantly different between controls and CAD subjects. The number of individuals carrying QQ genotype and Q allele was significantly higher in controls than patients (55.6 vs. 33 % for QQ and 72.7 vs. 56.6 % for Q, respectively), while the number of subjects with QR and RR genotype and R allele was significantly higher in patients than in controls (47 vs. 34.3 % for QR, 19.8 vs. 10 % for RR, and 43.4 vs. 27.3 % for R, respectively). Among the control subjects, Q and R were found to be major and minor alleles, respectively (73 vs. 27 %). The distribution of genotypes in cases ($\chi^2 = 0.204$, $p = 0.651$) and controls ($\chi^2 = 2.033$, $p = 0.154$) was found to be in accordance with the Hardy–Weinberg equilibrium.

Association of Q192R with CAD risk

We also determined the association of QR and RR genotypes and R allele with CAD risk. The odds ratios (ORs) for QR and RR genotypes with CAD risk were 2.3 (95 % CI 1.3–4.1, $p < 0.01$) and 3.2 (95 % CI 1.4–7.4, $p < 0.01$), respectively, and for the R allele, it was 2.04 (95 % CI 1.4–3.0, $p < 0.005$) compared to QQ genotype and Q allele (Table 2). The association of Q192R polymorphism with CAD risk was further tested by multiple logistic regression analysis for its independence from other risk factors (Table 3). Age (ORs 1.44, 95 % CI 1.1–1.83, $p < 0.05$), male gender (ORs 1.41, 95 % CI 1.1–1.72, $p < 0.05$), smoking (ORs 1.2, 95 % CI 1.0–1.34, $p < 0.05$), diabetes (ORs 1.17, 95 % CI 1.0–1.32, $p < 0.05$), BMI (ORs 1.32, 95 % CI 1.08–1.61, $p < 0.05$), systolic blood pressure (ORs 1.51, 95 % CI 1.05–2.1, $p < 0.05$), triglycerides (ORs 1.21, 95 % CI 1.1–1.4, $p < 0.05$), HDL-cholesterol (ORs 0.65, 95 % CI 0.48–0.87, $p < 0.01$), total cholesterol (ORs 1.15, 95 % CI 1.04–1.3, $p < 0.05$), and LDL-cholesterol (ORs 1.23, 95 % CI 1.1–1.33, $p < 0.05$) were all associated with CAD risk. Association of QR (ORs 2.03, 95 % CI 1.42–2.89, $p < 0.005$) and RR (ORs 3.42, 95 % CI 2.09–5.58, $p < 0.001$) genotypes with CAD risk remained significant even after accounting for these risk factors.

Genotype-based distribution of characteristics

To study the effects of Q192R polymorphism on anthropometric, clinical, and biochemical parameters, we analyzed the distribution of these variables in relation to QQ, QR, and RR genotypes. The analysis revealed that RR genotype in comparison with QQ was significantly associated with elevated BMI (32.4 ± 4.7 vs. 27.3 ± 5.4 kg/m^2, $p < 0.001$), systolic blood pressure (132.3 ± 21.7 vs. 121.2 ± 19.2 mmHg, $p < 0.005$), fasting glucose (7.4 ± 1.5 vs. 5.2 ± 1.3 mmol/l, $p < 0.05$), total cholesterol (4.8 ± 1.0 vs. 4.4 ± 0.95 mmol/l, $p < 0.05$), triglycerides (1.7 ± 0.85 vs. 1.5 ± 0.85 mmol/l, $p < 0.05$), and LDL-cholesterol (3.6 ± 1.0 vs. 3.4 ± 0.99 mmol/l, $p < 0.05$) (Table 4). On the contrary, the RR genotype was significantly related to a decreased HDL-cholesterol compared to that of QQ (0.86 ± 0.34 vs. 1.2 ± 0.35 mmol/l, $p < 0.001$) (Table 4).

Discussion

Increased oxidative stress or an impaired antioxidant defense mechanism can play a crucial role in the onset and progression of several chronic diseases. Oxidation of low-density lipoprotein (LDL) and the subsequent generation of lipid hydroperoxides accelerate the development of atherosclerosis [39, 40]. Consequently, emphasis has been placed on identifying the physiological targets with promising antioxidant activity. PON1, which resides in HDL-cholesterol particles, possesses antioxidant properties and has been widely studied at the genotypic and phenotypic levels for its ability to negate the oxidative damage and lower the risk of atherosclerosis [14]. In the present study, we tested whether the well-investigated PON1 coding region polymorphism Q192R is proatherogenic and whether it would be informative in predicting CAD status in Saudi subjects.

There are reported differences in the distribution of Q and R alleles with regard to their major and minor allele

Table 3 Multiple logistic regression analysis of the association of q192r polymorphism with CAD risk

Parameters	β	SE	ORs (95 % CI)	p value.
Age (years)	0.37	0.12	1.44 (1.1–1.83)	<0.05
Gender (M/F)	0.35	0.10	1.41 (1.1–1.72)	<0.05
Smoking Status(Y/N)	0.20	0.05	1.2 (1.0–1.34)	<0.05
Diabetic Status(Y/N)	0.16	0.06	1.17 (1.0–1.32)	<0.05
BMI (kg/m^2)	0.28	0.10	1.32 (1.08–1.61)	<0.05
SBP (mmHg)	0.41	0.18	1.51 (1.05–2.1)	<0.05
HDL-cholesterol (mmol/l)	−0.43	0.15	0.65 (0.48–0.87)	<0.01
Total cholesterol (mmol/l)	0.14	0.05	1.15 (1.04–1.3)	<0.05
LDL-cholesterol (mmol/l)	0.21	0.04	1.23 (1.1–1.33)	<0.05
Triglycerides (mmol/l)	0.19	0.06	1.21 (1.1–1.4)	<0.05
Q192R polymorphism				
QR[a]	0.71	0.18	2.03 (1.42–2.89)	<0.005
RR[a]	1.23	0.25	3.42 (2.09–5.58)	<0.001

p value significant at <0.05

β coefficient, *SE* standard error

* Reference to QQ genotype

Table 4 Distribution of patient characteristics according to Q192R genotypes

Parameters	QQ	QR	RR	p value
N	100	94	35	
Age (years)	48.3 ± 15.1	52.4 ± 13.0	53.3 ± 12.9	0.07
BMI (kg/m^2)	27.3 ± 5.4	30.8 ± 6.2	32.4 ± 4.7	<0.001
SBP (mmHg)	121.2 ± 19.2	128.1 ± 17.4	132.3 ± 21.7	<0.005
DBP (mmHg)	78.8 ± 11.7	78.7 ± 10.7	78.7 ± 13.4	0.86
Glucose (mmol/l)	5.2 ± 1.3	7.2 ± 1.5	7.4 ± 1.5	<0.05
Insulin (μIU/ml)	11.5 ± 1.8	16.2 ± 1.6	12.8 ± 1.5	0.41
HDL-cholesterol (mmol/l)	1.2 ± 0.35	0.96 ± 0.32	0.86 ± 0.34	<0.001
Total cholesterol (mmol/l)	4.4 ± 0.95	4.7 ± 1.0	4.8 ± 1.0	<0.05
LDL-cholesterol (mmol/l)	3.4 ± 0.99	3.5 ± 1.0	3.6 ± 1.0	<0.05
Triglycerides (mmol/l)	1.5 ± 0.85	1.6 ± 0.86	1.7 ± 0.85	<0.05

p value significant at <0.05

BMI body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *CAD* coronary artery disease

states in different ethnic populations. Among the control subjects, we found Q and R to be major and minor alleles at codon 192 in the PON1 gene, respectively. Thus, the distribution of Q and R allele of the PON1 gene in the Saudi control population tended to be closer to that observed in Caucasians [20, 41–43], Asian Indians [29], Turkish [38], and Egyptian [44], but differed from that of Japanese [26, 45], Chinese [46], and Hispanic [47] populations where the R allele was predominant. Importantly, the Q and R allele distributions observed in this study confirm a previous, independent study carried out in the Saudi population, where the phenotypic frequencies (paraoxonase/arylesterase activity ratio) suggested that the low-activity phenotype (Q allele) was the major and the high-activity phenotype (R allele) the minor allele [48]. It is clear from the comparison (Table 5) of allele frequencies in different populations that major and minor allele frequencies differ significantly among ethnically different populations and may thus contribute to the differences in the association of Q and R alleles with the disease risk. Additionally, these variations also underscore the possibility of environmental and demographic factors altering the disease risk, independent of genetic variability.

We found a significantly increased frequency of QR and RR genotypes in CAD patients compared to controls and accordingly a significant association of the Q192R polymorphism with CAD risk in the population studied, indicating that the PON1 gene may play a crucial role in CAD pathology. Logistic regression analysis adjusting for age, gender, dyslipidemia, hypertension, smoking, and obesity revealed an independent relation of Q192R with CAD risk. However, the possibility of confounding factors, other than

Table 5 Allele frequencies of PON1 gene Q192R polymorphism in different populations

Population	*N*	Q912R polymorphism		Ref
		Q allele (%)	R allele (%)	
Caucasian	282	71	29	[20]
Japanese	132	40	60	[45]
Chinese	475	35	65	[46]
Hispanic	214	51	49	[47]
Asian Indian	165	67	33	[29]
Turkish	142	74	26	[38]
Egyptian	50	63	37	[44]
Saudi Arabian	108	73	27	PS

PS present study

those accounted here, contributing to the disease risk cannot be ruled out. To further derive support for the role of Q192R in CAD development, we analyzed the distribution of confounding factors according to Q192R genotype. We found the QR and RR genotypes to be significantly associated with older age, obesity, male gender, elevated systolic blood pressure, triglycerides, LDL- and total cholesterol, and reduced levels of HDL-cholesterol. Thus, the shift of the levels of these parameters in QR and RR carriers closer to the values that signal the impending risk of atherosclerosis suggests the possible participation of the Q192R polymorphism in CAD etiology [44, 49].

The Q192R polymorphism in the PON1 gene impedes the ability of PON1 to inhibit LDL oxidation, suggesting that the R192 allele is less effective than Q192 in preventing LDL oxidation [18, 19, 24, 50]. Likewise, the ability of recombinant PON1 to prevent LDL oxidation is decreased due to the presence of arginine in place of glutamine, reflecting the expected effect of the Q192R polymorphism [51]. Additionally, subjects with the RR genotype are prone to experience coronary spasms, which reflects endothelial dysfunction related to oxidative damage, providing further support that the R allele could increase the susceptibility to CHD [52]. It was reported that the PON1 active site required for protection against LDL oxidation is different from the one required for its arylesterase/paraoxonase activities, suggesting that the R allele, despite showing higher activity toward paraoxon, is defective as it impedes its antioxidant activity toward LDL, due to its active site modulating effect [19]. Thus, carriers of the R allele possess reduced ability to prevent the oxidative modification of LDL and consequently are more susceptible to develop CAD than carriers of the Q allele. There are studies that previously examined the association of the Q192R polymorphism with CAD risk; however, the data have been inconsistent. While several studies found a positive correlation of Q192R with CAD risk [23–30], others have not [31–38]. A recent meta-analysis of 88 studies comprising 24,702 CAD cases and 38, 232 controls revealed per-allele odds ratio (ORs) for CAD for 192R to be 1.11 (95 % CI 1.05–1.17) and similar results were found for QR (ORs 1.14) and RR (ORs 1.17) genotypes, indicating a significant association of Q192R polymorphism with the disease risk [53]. The disparity in the data in relating Q192R with CAD risk might have stemmed from the differences in ethnicity, sample size, subject recruiting criteria, gene–gene and gene–environmental interactions and applied genotyping methods [13, 14, 24, 54, 55].

Unlike the association studies at a genetic level, the majority of studies dealing with PON1 activity measurements have consistently found reduced PON1 activity in the CAD patients versus control subjects [56]. Accordingly, these studies have related the reduced PON1 activity/concentration with an increased atherosclerosis risk, strongly endorsing the reliability of measuring PON1 activity to determine the presence of CAD. It has also been prospectively demonstrated that measuring the PON1 activity is informative in predicting future CAD risk [57]. However, far fewer studies failed to replicate these observations [31, 58]. Although in the present study we did not measure PON1 activity, the higher frequency of RR genotypes in the cases versus controls underscores the diagnostic value of genotyping for Q192R polymorphism in the cohort studied. Besides its diagnostic value, the higher RR genotypes in the patient category also suggest the possible role of Q192R polymorphism in CAD initiation and progression, presumably due to reduced ability of PON1 with the R allele in preventing oxidative modification of LDL.

In conclusion, this is the first study to determine the distribution and frequency of Q192R polymorphism of the PON1 gene and its association with CAD risk in Saudi subjects. Further studies with larger sample size evaluating additional PON1 polymorphisms, haplotypes, and, importantly, PON1 activity may comprehensively provide the significance of genotype and phenotype applications in determining and predicting CAD risk in this population.

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Conflict of interests Authors declare no conflicts of interests.

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