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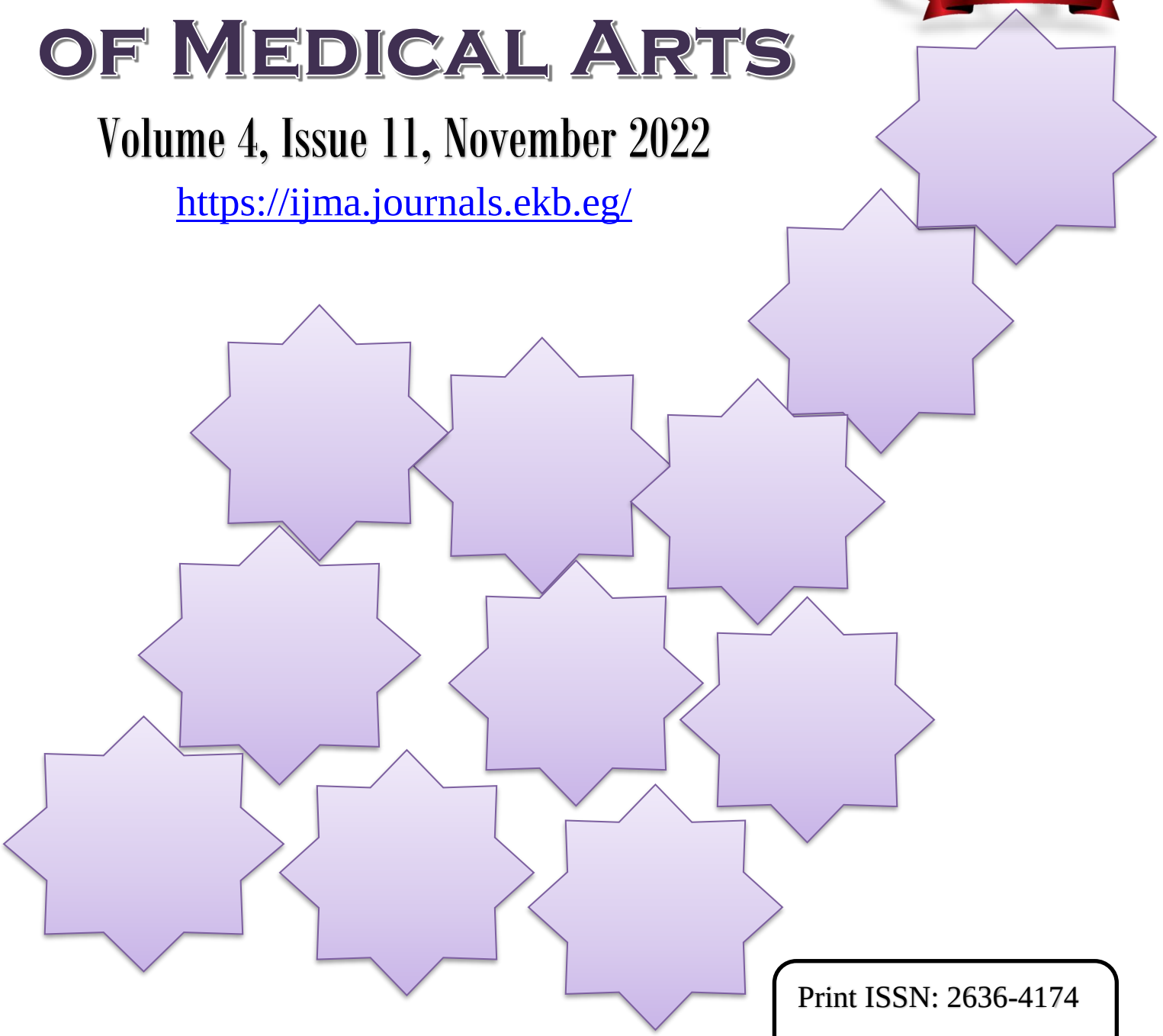

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Original Article

Paraoxonase 1 Gene Polymorphisms as A Risk Factor of Coronary Artery Diseases

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ABSTRACT

Background: The most prevalent form of heart disease is coronary artery disease [CAD], which is currently one of the leading causes of death in the world and is predicted to remain that way for the next 20 years. Atherosclerosis, genetic predisposition, environment and lifestyle are the main risk factors for CAD. Paraoxonase1 [PON1] is a glycoprotein enzyme associated with high-density lipoprotein [HDL] particles in the blood. It can prevent lipid oxidation, lowering the risk of atherogenesis, by doing so.

The aim of the work: This work aims to study the frequency of association of PON1 gene polymorphism and risk of coronary artery diseases. This could help in better understanding of molecular basis and pathogenesis of coronary artery disease.

Patients and Methods: The study included 80 subjects, 40 patients who admitted in Al-Azhar medical hospital in Damietta with established diagnosis of coronary artery disease by coronary angiography and 40 healthy participants. Genotyping of PON1 Q192R [A/G] was done.

Results: A statistically significant association was observed with AG and GG genotypes of PON1 gene with CAD with P= 0.017. The G allele of PON1 was higher in CAD patients than controls suggesting that this allele may demonstrate a susceptibility effect to CAD in our cohort with P=0.025.

Conclusion: The Q192R polymorphism in the PON1 gene may be a susceptibility gene associated with increased risk of CAD among Egyptians.

Keywords: Paraoxonase 1 [PON1]; Coronary artery disease; Genetic polymorphism.

INTRODUCTION

Coronary artery disease [CAD] is one of the cardiovascular diseases, which is brought on by inadequate blood and oxygen delivery to the heart [1]. Myocardial infarction, unstable angina [UA], stable angina, and sudden cardiac death are all forms of CAD. It ranks among the leading causes of death for both men and women. The World Health Organization estimates that over 17.9 million individuals worldwide pass away from CAD each year [2]. CAD is one of the clinical manifestations of atherosclerosis. The development of CAD is significantly influenced by environmental and genetic variables. The main risk factors for CAD include age, diabetes, high blood pressure, family history, and hyperlipidemia. Numerous gene variants have been discovered to be independent risk factors for CAD [3].

The family of Paraoxonase [PON] contains three enzymes that are mainly lactonases they are mainly PON1, PON2, PON3 [4]. PON genes are located adjacent to each other on chromosomes 7q21-22 [5]. PON1 is a 355 amino acid [a.a] glycoprotein that is made in the liver and released into the bloodstream, where it is linked to HDL. Most of the HDL's antioxidant action on preventing low-density lipoprotein oxidation is attributed to PON1 [6]. In the future, macrophage PON1 binding sites may be the focus of cardioprotective therapy because PON1 and HDL-associated PON1 mostly bind to macrophages and have antiatherogenic effects. For effective therapy and to prevent atherosclerosis, research into the relationships between PON1, antioxidants, and macrophages is also helpful [7]. Increased LDL oxidation, increased macrophage oxidative stress, and enlarged atherosclerotic lesion are all associated with genetic deletion of PON1 in atherosclerotic animal models. [8]. On the other hand, transgenic mice that overexpress the human PON1 gene had less aortic lesions [9].

El-Lebedy *et al.* [10] hypothesized that PON1 Q192R polymorphism is related to CVDs, PON1 lower serum concentration, and may be a CVD risk factor in Egyptian patients with type 2 diabetes mellitus. In contrast, **Birjmouhn *et al.*** [11] demonstrate that Q192R polymorphism of PON1 gene highly affects PON1 activity but it was not associated with CAD in the future. The purpose of this study is to investigate the frequency of association between PON1 gene polymorphism and coronary artery disease risk. This could help with a better understanding of the molecular basis and pathogenesis of coronary artery disease.

PATIENTS AND METHODS

This study was a case-control study that included 80 subjects: 40 patients who were admitted to Al-Azhar Medical Hospital in Damietta with an established diagnosis of coronary artery disease by coronary angiography and 40 healthy participants. This study was carried out in the Medical Biochemistry Department, Damietta Faculty of Medicine, Al-Azhar University, during 2020–2021 with appropriate consent to participate in this study after an explanation to patients of how much it is helpful for humanity.

Inclusion Criteria: Patients included were diagnosed with coronary artery disease, coronary angiography that showed 70% stenosis in one or more coronary arteries were considered to have CAD.

Exclusion Criteria: The following patients were excluded from this study: patients with congenital heart disease, rheumatic heart disease, cancer, septicemia, dysthyroidism, undergoing hormonal treatment, and renal failure [creatinine clearance <40 mL/min].

Both patients and controls were subjected to: Full history taking, full clinical examination. Patients were subjected to coronary angiography. Laboratory investigations were done. After a 12-hour overnight fast, blood samples [5ml] were taken from the antecubital vein of patients and control individuals between 8 and 10 a.m. Each sample was divided as following: a] 2 ml were delivered to a test tube containing 200 µl EDTA to prevent blood coagulation and stored at -20 °C until DNA extraction for genotyping. b] 3 ml of blood was collected in sterilized dry tube for the lipid profile, random blood glucose, creatinine, and liver function tests.

Typing of PON1 Q192 R [rs 662] gene polymorphisms: Whole venous EDTA blood was used to obtain genomic DNA using INTRON G-spin™ Total DNA Extraction Kit. The PON1 Q192 R [rs 662] polymorphism was genotyped by PCR based restriction fragment length polymorphism [RFLP], according to the method of **Humbert *et al.*** [12].

Alanine transaminase [ALT] and Aspartate transaminase [AST] were assayed spectrophotometrically using chemistry auto analyser according to the method of **Bergmeyer *et al.*** [13]. Determination of the serum Glucose according to the methodology of **Caraway and Watts** [14]. Determination of lipid profile was according to the methodology of **Jalali *et al.*** [15]. Determination of creatinine was according to **Jaffe's** method [16].

Statistical analysis: Using SPSS 22.0 for Windows [SPSS Inc., Chicago, IL, USA] and MedCalc 13 for Windows [MedCalc Software bvba, Ostend, Belgium], all data were gathered, tabulated, and statistically evaluated. Using the Shapiro Walk test, the distribution of the data was examined for normality. Frequencies and relative percentages were used to depict qualitative data. The difference between the qualitative variables was calculated using the chi square test [X^2] and Fisher exact. The mean and SD [standard deviation] were used to express quantitative data. For parametric and non-parametric variables, respectively, the Independent t test and the Mann-Whitney test were employed to calculate the difference between quantitative variables in two groups. The predictors of CAD in patients were identified using regression analysis utilizing the stepwise approach. The significance level for all statistical comparisons was two tailed. Level of P-value 0.05 denotes a significant difference.

RESULTS

Regarding age and BMI, cases group were significantly older and had higher BMI [P=0.001]. Regarding comorbidities, there is a substantial difference between the groups regarding smoking, HTN, dyslipidemia, and MI. Patients in the cases group had significantly increased heart rate, SBP, and DBP. TC, TG, LDL and lower HDL [table 1].

Table [2] demonstrates that the G allele, AG and GG phenotypes were more frequent in the cases group with significant difference.

Table [3] demonstrates that there are no significant differences between the genotyping subgroups for TC, TG, HDL, and LDL among the case groups.

Table [4] demonstrates that, among the two main analyzed groups, there is no statistically significant difference between the two allele groups for TC, TG, HDL, and LDL.

Table [5] shows that Age, male gender, DM, smoking, TC, TG and LDL were found to be significant determinants of coronary artery disease in patients.

Figure [1] shows visualization of RFLP analysis of rs662 polymorphism, 3% agarose gel electrophoresis; three bands in lane 6, 9 and two bands in lane 3,4 and 8].

Table [1]: Demographic, clinical and laboratory data of the studied groups

		Cases [n=40]	Controls [n=40]	t / χ^2	P
Age [years] Mean ± SD		52.43 ± 5.17	48.67 ± 4.39	3.51	**0.001**
Sex	Male Female	27 [67.5%] 13 [32.5%]	27 [62.5%] 13 [37.5%]	0.219	0.639
BMI [kg/m^2] Mean ± SD		28.88 ± 1.46	24.36 ± 1.32	14.5	**0.001**
Comorbidities	Smoking	21	11	5.21	**0.001**
	Diabetes mellitus	13	6	3.38	0.066
	Hypertension	11	4	4.02	**0.001**
	Dyslipidemia	14	3	9.04	**0.001**
	Myocardial infarction	12	0	14	**0.001**
Heart rate [beat/min] Mean ± SD		92.27 ± 7.42	88.65 ± 5.87	2.42	**0.001**
SBP [mmHg] Mean ± SD		134.45 ± 8.39	122.51 ± 7.64	6.65	**0.001**
DBP [mmHg] Mean ± SD		79.63 ± 3.59	75.81 ± 4.38	4.27	**0.001**
Hb [g/dL] Mean ± SD		11.59 ± 2.08	12.14 ± 2.15	1.16	0.249
RBS [mg/dL] Mean ± SD		120.45 ± 14.73	124.96 ± 12.65	1.47	0.146
Creatinine [mg/dL] Mean ± SD		0.903 ± 0.235	0.822 ± 0.193	.168	0.096
ALT [U/L] Mean ± SD		34.58 ± 10.89	32.65 ± 9.23	.855	0.395
AST [U/L] Mean ± SD		30.41 ± 9.49	28.3 ± 7.52	1.1	0.274
TC [mg/dL] Mean ± SD		227.34 ± 52.49	164.62 ± 22.88	6.93	**0.001**
TG [mg/dL] Mean ± SD		163.12 ± 45.27	114.29 ± 20.18	6.23	**0.001**
HDL [mg/dL] Mean ± SD		39.38 ± 16.82	56.68 ± 9.69	5.64	**0.001**
LDL [mg/dL] Mean ± SD		108.81 ± 46.48	69.15 ± 19.52	4.98	**0.001**

Table [2]: Genotyping and Allele distribution of the two studied groups

		Cases [n=40]	Controls [n=40]	X^2	P
Genotyping	AA AG GG	20 [50%] 13 [32.5%] 7 [17.5%]	32 [80%] 6 [15%] 2 [5%]	8.13	**0.017***
Allele distribution	Allele A Allele G	53 [66 %] 27 [34 %]	70 [87.5 %] 10 [12.5 %]	5.0	**0.025***

Table [3]: Lipid profile parameters among cases group according to genotyping

	AA [n=20]	AG [n=13]	GG [n=7]	F	P
TC [mg/dL] Mean ± SD	232.93 ± 36.64	224.26 ± 31.56	213.37 ± 28.22	.919	.408
TG [mg/dL] Mean ± SD	181.4 ± 41.83	164.57± 37.88	150.31 ± 29.54	1.89	.166
LDL [mg/dL] Mean ± SD	120.95 ± 49.34	102.62 ± 34.65	91.78 ± 28.43	1.53	.229
HDL [mg/dL] Mean ± SD	35.61 ± 9.25	40.77 ± 9.48	44.81 ± 8.12	3.02	.061

Table [4]: Lipid profile parameters among the two studied groups according to Alleles

Cases	**Allele A [n=53]**	**Allele G [n=27]**	**t**	**P**
TC [mg/dL] Mean ± SD	234.51 ± 53.26	225.84 ± 48.59	.484	.631
TG [mg/dL] Mean ± SD	174.34 ± 47.62	161.55 ± 40.26	.813	.421
HDL [mg/dL] Mean ± SD	38.21 ± 12.93	46.57 ± 10.75	1.96	.057
LDL [mg/dL] Mean ± SD	114.39 ± 41.62	98.73 ± 38.66	1.11	.273
Controls	**Allele A [n=70]**	**Allele G [n=10]**	**t**	**P**
TC [mg/dL] Mean ± SD	168.23 ± 24.65	165.74 ± 21.73	.303	.764
TG [mg/dL] Mean ± SD	113.67 ± 21.35	118.26 ± 24.68	.595	.556
HDL [mg/dL] Mean ± SD	54.28 ± 8.67	57.33 ± 10.58	.954	.346
LDL [mg/dL] Mean ± SD	72.54 ± 20.15	68.27 ± 18.49	.629	.533

Table [5]: Multivariate logistic regression analysis of determinants of coronary artery disease in patients

	OR	S.E.	Sig.	95% Confidence Interval
Age	1.063	0.152	**0.001**	1.021 - 1.122
Male gender	2.264	0.089	**0.034**	.649 – 4.164
Smoking	.913	0.062	**0.001**	.716 - .943
HTN	1.012	0.161	0.216	.816 - 1.035
DM	2.233	0.046	**0.001**	.495 – 3.642
TC	1.257	7.572	**0.001**	1.019 - 1.550
TG	1.295	4.315	**0.001**	.836 - 1.387
LDL	1.267	2.613	**0.001**	.951 - 1.688
HDL	.574	0.359	0.112	.026 - .681

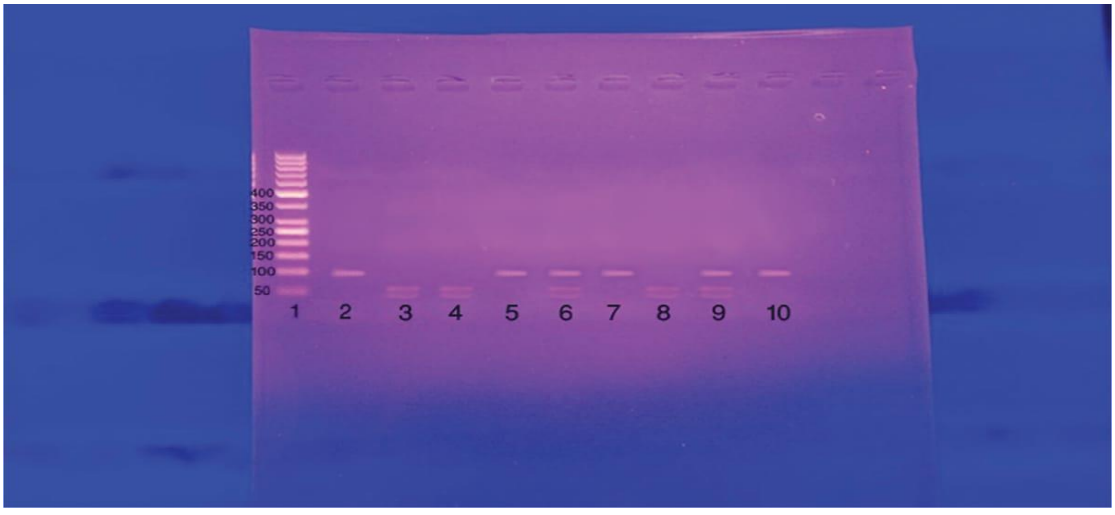

Figure [1]: Visualization of RFLP analysis of rs662 polymorphism, 3% agarose gel electrophoresis; three bands in lane 6, 9 and two bands in lane 3,4 and 8]

DISCUSSION

The major cause of death globally is now cardiovascular disease. It caused 151 million lost disability-adjusted life years [DALYs] and 17 million estimated deaths [around 30.0% of all deaths and 14.0% of all DALYs lost]. Additionally, CAD is the greatest cause of illness, disability, and mortality globally, accounting for 12.2% of global fatalities [7.2 million] [17]. Since the 1990s, CAD has been the main reason for early death in Egypt. CAD accounted for 46.2% of all deaths in Egypt in 2017 total mortality [18]. The interplay of hereditary and environmental variables leads to coronary artery disease. One of the fundamental processes that contributes to the development of CAD is the rise in lipid peroxidation. [19]. PON1 is a 43 kDa calcium-dependent glycoprotein with 355 amino acid residues. After being synthesized in the liver, PON1 is released into the bloodstream and mostly detected in HDLs, with smaller amounts being present in chylomicrons and very low-density lipoproteins.

PON1 is transferred from the liver to several tissues where it attaches to cell membranes and shields lipids against oxidation. PON1 also inhibits LDL oxidation and the inflammatory response [20]. Our study was carried out on 40 patients who were diagnosed formerly with CAD and admitted to Cardiology Unit in Al-Azhar Medical Hospital in Damietta and 40 age matched non-cardiac subjects. At first PON1 Q192R [A/G] genotyping was done, then lipid profile was done for the patient and control groups spectrophotometerically.

According to analysis of genotype frequency for PON1 Q192R polymorphism there is statistically significant difference between CAD patients and controls with higher prevalence of GG genotype and the G [R] allele of PON1 Q192R [A→G] polymorphism in CAD patients.

This agrees with **Corredor-orlandelli *et al.*** [21] who revealed that PON1.Q192R is a potentially helpful marker for CAD risk in the Colombian population**.** Also, **Kumar *et al.*** [22] founded that PON1 Q192R gene polymorphism is highly linked to CAD susceptibility in the North Indian population**.** Also, similar results were reported by **Ashiq *et al.*** [23] who concluded that the PON1 genetic polymorphism has a significant impact on coronary artery disorders. By varying its impact on several anthropometric and biochemical markers, this PON1 polymorphism may lead to the development of the CAD. Likewise, in studies conducted on Chinese population it was found that PON1 Q192R variant is associated with an increased risk for both CHD [24]. our results also coincide with those done by **Kaur *et al.*** [25] who founded that the Q192R polymorphism in the PON1 gene may be a susceptibility gene associated with increased risk of CAD in an Asian Indian population**.**

On the other hand, **Gupta *et al.*** [26] said that PON1 Q192R gene polymorphism in the North Indian population is not linked to an elevated risk of acute ischemic stroke. PON1 Q192R gene polymorphism requires more research with a bigger sample size before it can be regarded as a genetic risk factor for ischemic stroke. Furthermore, because of the limited correlation between Q192R polymorphisms and the risk of CAD, **Godbole *et al.*** [27] did not recommend PON1 genotyping as a clinical tool for CAD risk prediction. Also, **Martínez-Quintana *et al.*** [28] found no significant differences between the AA and AG/GG genotypes neither in clinical variables nor in the extent of coronary artery disease. Similarly, **Hernandez-Diaz *et al.*** [29] who concluded that there was no association observed between the risk of coronary heart diseases and the Q192R gene polymorphism of PON1.

Conclusion: The PON1 gene's Q192R polymorphism may be a susceptibility gene linked to an elevated risk of CAD in Egyptians.

Conflict of Interest and Financial Disclosure: None

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