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HINDIII AND S447X POLYMORPHISMS OF LIPOPROTEIN LIPASE GENE AND THEIR RELATIONSHIP TO CORONARY ARTERY DISEASE

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ABSTRACT

Coronary artery disease (CAD) is a leading cause of morbidity and mortality worldwide. Lipoprotein lipase is a key enzyme in lipoprotein metabolism and its gene is a major candidate gene for coronary heart disease. The aim of the present work was to study the association of HindIII and S447X polymorphisms in lipoprotein lipase gene with coronary artery disease and their impact on lipid metabolism. The study was conducted on 60 patients with CAD as defined by coronary angiography in addition to 50 apparently healthy subjects serving as a control group. Lipoprotein lipase gene polymorphism (HindIII and S447X) detection was done by polymerase chain reaction– restriction fragment length polymorphism (PCR- RFLP) technique. The present study revealed that the studied population was in Hardy- Weinberg equilibrium (HWE). HindIII polymorphism frequency did not differ between patients and controls. Meanwhile, the S447X polymorphism (SX genotype and the X allele) was more frequent in controls as compared to CAD patients. Carriers of X allele and H^-X haplotype had lower triglyceride levels and higher HDL-C levels as compared to those with absent X allele and H^+S haplotype. Meanwhile H^- allele was not associated with any change in lipid profile. In conclusion, the S447X polymorphism can be considered as one of the protective factors against development of CAD. Meanwhile, HindIII polymorphism failed to prove any association with CAD.

Keywords: Coronary artery disease; lipoprotein lipase; HindIII polymorphism; S447X polymorphism; PCR; RFLP

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INTRODUCTION

Coronary artery disease (CAD) is one of the greatest causes of morbidity and mortality worldwide being responsible for a high percentage of death annually in different countries (Al-Jafari et al., 2012). CAD is a multifactorial disorder believed to result from an interaction between the genetic background and environmental factors such as diet, smoking and physical activity (Daoud et al., 2013). The disease is usually associated with conventional risk factors including hypertension, diabetes mellitus, dyslipidemia and smoking (Rustempasic et al., 2014). In recent years, many studies started to explore the relationship between CAD and the common variants of genes central to lipid metabolism (Al-Jafari et al., 2012 andTurlo et al., 2014).

The lipoprotein lipase (LPL) gene, which spans; 35 kilobases on chromosome 8p22 is composed of 10 exons separated by 9 introns and encodes the mature form of LPL (Tanguturi et al., 2013). LPL is the rate-limiting enzyme in the hydrolysis of triglyceride (TG)- rich lipoprotein particles (chylomicrons and very-low-density lipoprotein) resulting in the production of free fatty acids (FFAs) and taking part in the initiation of high density lipoprotein cholesterol (HDL-C) maturation through the exchange of apoproteins C and E between TG-rich lipoproteins and HDL-C (Munshi et al., 2012 and Baik et al., 2013). Independent of its lipolytic activity, LPL binds to and travels with chylomicron remnants to the liver, where it enhances the clearance of these lipoproteins via low density lipoprotein (LDL) receptors (Daoud et al., 2013). Due to the pivotal role of LPL in lipid metabolism, genetic defects in the LPL gene can affect lipoprotein metabolism, resulting in an atherogenic lipid profile. Several restriction fragment length polymorphisms (RFLPs) have been identified in the coding and non-coding regions of the gene; however, there is controversy with regard to the effects of these variants on LPL activity (Mu˜noz-Barrios et al., 2012 and Zambrano et al., 2014).

The HindIII polymorphism is an intronic base transition of thymine (T) to guanine (G) at position 495 in intron 8 and thus abolishes a HindIII restriction enzyme recognition site (Tanguturi et al., 2013). The S447X polymorphism is characterized by cytosine-to-guanine transversion at position 1595 in exon 9, resulting in a premature stop

codon that truncates the protein due to the loss of the C-terminal serine and glycine (Chen et al., 208). LPL polymorphisms effects on lipids and coronary artery disease are controversial among studies and populations and evidence is still limited (Rebhi et al., 2012).

The aim of the present work was to study the association of HindIII and S447X polymorphisms in LPL gene with coronary artery disease and their impact on lipid metabolism.

MATERIALS AND METHODS

This study was conducted in the Angiography Unit of Cardiology Department in Ain Shams University Hospitals, Cairo- EGYPT. The work described has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki). The study was approved by the Ethics Committee of the Faculty of Medicine of Ain Shams University and all participants gave their informed written consent. The study included 60 Egyptian patients with CAD as defined by coronary angiography in addition to 50 apparently healthy subjects serving as a control group.

Five milliliters of venous blood were withdrawn under complete aseptic conditions subsequent to an overnight fast from patients (prior to angiography) and healthy controls. Three mL of blood were put in a sterile plain vacutainer and left to clot for 30 minutes, centrifuged (at 1000xg for 10 minutes) and the separated serum was used for the assay of lipid profile. The remaining two milliliters of blood were put in a sterile EDTA vacutainer for HindIII and S447X polymorphism detection.

Lipid profile (Total cholesterol, TG and HDL-C) were analyzed on the Synchron CX-9 Pro Auto-analyzer (Beckman Coulter, Inc. Fullerton, CA 92835-3100, USA) by enzymatic method, while LDL-C was calculated using Friedwald equation.

Lipoprotein lipase gene polymorphisms (HindIII and S447X) *DNA extraction* was performed using whole blood genomic DNA extraction kit supplied by QIAamp DNA Blood Mini kit (Q1AGEN Incorporation, USA) and kept at -20° C until required. The presence of HindIII and S447X polymorphisms was determined by *polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP). Amplification by PCR* was performed in a DNA thermocycler (9700 Applied Biosystem PCR). The test primers were prepared by

Bioneer (Bioneer corp, South Korea). For the HindIII polymorphism, the forward primer was 5'-GATGTCTACCTGGATAATCAAAG-3' and the reverse primer was 5'-CTTCAGCTAGACATTGCTAGTGT-3'. For S447X polymorphism, the forward primer was5'-TACACTAGCAATGTCTAGCTGA-3' and the reverse primer was 5' TCAGCTTTAGCCCAGAATGC-3'. The reaction mixture consisted of 5 µL DNA extract, 2.5 µL forward primer, 2.5 µL reverse primer, 25 µL deionized water and 15 µL master mix (ready to use) formed of Dream Taq DNA polymerase, optimized Dream Taq Green buffer, $MgCl_2$ and deoxynucleotide triphosphates (dNTPs). The master mix was supplied by Fermentas (Fermentas, USA). For HindIII polymorphism, The PCR conditions were as follows: an initial 5-min denaturation at 96° C, 40 cycles of denaturation at 94° C for 1 min, annealing at 57° C for 1 min and extension at 72° C for 1 min, with a final extension at 72° C for 7 min. Samples were digested by fastDigest HindIII restriction enzyme supplied by fermentas (Fermentas, USA). The common H^+ allele has one restriction site and produces two fragments of 210 and 140 bp. For S447X polymorphism, The PCR conditions were as follows: 5 min at 94° C, 40 cycles of denaturation for 1 min at 94°C, annealing for 1 min at 60°C and extension for 30 sec. at 72° C, and a final extension for 7 min at 72° C. Samples were digested using MnII restriction enzyme supplied by fermentas. (Fermentas, USA). The polymorphic X allele has two restriction sites and produces three fragments of 285, 250 and 203 bp. *DNA detection* was performed by 2% agarose gel electrophoresis and stained by ethidium bromide (Figures 1 and 2).

Statistical analysis

Statistical analysis was performed using statistical software program SPSS version 9.02. Qualitative data were expressed as number and percent (n; %); parametric quantitative data were expressed as mean and standard deviation (SD) while non-parametric quantitative data were expressed as median and interquartile range (IQR). Comparative statistics between two independent groups were done by The Chi squared Test (X^2) for qualitative data, Student’s t test for quantitative parametric data and Wilcoxon’s rank sum for quantitative non parametric data. Genotype distribution was investigated in relation to Hardy-Weinberg equilibrium (HWE) by applying Chi squared Test (X^2). $p<0.05$ was considered significant.

RESULTS

Descriptive and comparative statistics of the demographic and laboratory data among all CAD patients versus healthy controls are included in **table 1.** Hypertension, smoking and diabetes mellitus were more frequent in CAD patients compared to the control group ($p<0.05$, respectively). Moreover, CAD patients had significantly higher total cholesterol and LDL-C and significantly lower HDL-C as compared to controls ($p<0.05$ respectively).

The population included in the study was genotyped for the two LPL gene polymorphisms (Figure 3). Testing deviation from the HWE was performed by chi-squared test, using the observed genotype frequencies obtained from the data and the expected genotype frequencies obtained from the Hardy- Weinberg principle. For all polymorphisms in the patients and controls, the distribution of genotypes yielded from the HWE was as expected ($p >0.05$ respectively).

The descriptive and comparative statistics of the genotype and allele frequency of the studied polymorphisms in patients and controls are presented in **table 2.** As regards the HindIII polymorphism, the (H^-H^-/ H^+H^-) genotypes and the H^- allele were less frequent in CAD patients as compared to controls; however, such difference in frequency was not statistically significant ($p>0.05$ respectively). As regards the S447X polymorphism, both the genotype and allele frequencies showed significant differences between both groups where the SX genotype and the X allele were more frequent in controls as compared to CAD patients ($p<0.05$ respectively). The genotype 447XX was not identified.

Table 3 shows the comparative statistics of the blood lipid levels according to the HindIII and the S447X polymorphisms of the LPL gene among all the studied groups. As regards the HindIII polymorphism, no significant difference was found in subjects having the H^- allele as compared to those with absent H^- allele ($p>0.05$, respectively). For S447X polymorphism, subjects having the X allele demonstrated a significantly lower TG and a significantly higher HDL-C as compared to those with absent X allele ($p<0.05$, respectively).

Haplotype reconstruction for the two LPL polymorphisms under study revealed the presence of 72 subjects with H^+S haplotype while the haplotype H^-X was present in only 20 subjects. Statistical comparison between H^+S and H^-X haplotypes revealed that subjects with H^+S had a significantly higher TG and a significantly lower HDL-C (P<0.05 respectively)as compared to H^-X haplotype subjects **(table 4).**

Table (1): Descriptive and comparative statistics of the demographic and laboratory data among all CAD patients versus healthy controls

Parameters	Patients Group (n=60)	Control Group (n=50)	t/Z•/x^2*
Age (years) Median; IQR	60.0 51.3 - 65.0	59.5 55.8 - 63.0	0.241•
Male sex (n; %)	51 (85%)	35 (70%)	3.597*
Presence of HTN (n; %)	35 (58.3%) $^{\Delta}$	18 (36%)	0.545*
History of Smoking (n;%)	27 (45%) $^{\Delta}$	13 (26%)	4.255*
Presence of diabetes (n;%)	26 (43.3%) $^{\Delta}$	9 (18%)	8.068*
T.Chol (mg/dL) Mean ±SD	189.5 ± 40.8$^{\Delta}$	173.3 ± 32.5	2.272
TG (mg/dL) Median (IQR)	114.0 (78.3 - 140.3)	101.5 (79.8 – 148.3)	0.354•
HDL-C (mg/dL) Median (IQR)	36.0$^{\Delta}$ (30.3 – 44.8)	54.0 (43.8 – 59.0)	5.601•
LDL-C (mg/dL)Mean ±SD	127.5 ± 37.1$^{\Delta}$	98.9 ± 28.3	4.576

CAD: coronary artery disease; HTN: hypertension; T. Chol: total cholesterol; TG: triglycerides; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; IQR: interquartile range; SD: standard deviation; Δ:p <0.05.

Table (2): Genotype and allele frequency of HindIII and S447X polymorphisms in patients and controls

Polymorphism Hind III	Genotype frequency (%)			Allele frequency (%)	
	H^+H^+	H^+H^-	H^-H^-	H^+	H^-
Patients (n=60)	16 (26.7%)	33 (55%)	11 (18.3%)	49(81.7 %)	44 (73.3%)
Controls (n=50)	6 (12%)	27 (54%)	17(34%)	33(66%)	44(88%)
X^2	5.568	5.568	5.568	3.528	3.667

Polymorphism S447X	Genotype frequency		Allele frequency
	SS	SX	X
Patients	50 (83.3%)	10 (16.7%)	10 (16.7%)
Controls	30 (60%)	20 (40%)	20 (40%)
X^2	7.486*	7.486*	7.486*

*: p<0.05

Table (3): Comparative statistics of the blood lipid levels according to the HindIII and the S447X polymorphisms of the LPL gene among all the studied groups

Lipid Profile	Hind III (n= 110)			S447X (n=110)		
	H^- allele Present (n=88)	H^- allele Absent (n=22)	t/Z•	X allele Present (n=30)	X allele Absent (n=80)	t/Z•
T.Chol (mg/dL) Mean ±SD	179.9 ± 36.2	191.1 ± 44.2	1.23	187 ± 30.6	180.3 ± 40.4	0.820
TG (mg/dL) Median IQR	99.5 (77.5 – 133.0)	127.5 (88.3 – 177.3)	1.91•	80.0 (69.8 – 98.8)	120.0 (89.5 – 154.3)	4.722•Δ
HDL-C (mg/dL) Median IQR	45.0 (34.3 – 55.0)	36.0 (30.8 – 50.3)	1.64•	55.5 (42.8 – 61.0)	39.0 (33 – 49)	4.090•Δ
LDL-C (mg/dL) Mean ±SD	112.4 ± 34.3	123.1 ± 42.8	1.25	116.3 ± 30.5	113.8 ± 38.2	0.323

LPL: lipoprotein lipase; T. Chol: total cholesterol; TG: triglycerides; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; IQR: interquartile range; SD: standard deviation; Δ:p: <0.05

Table (4): Descriptive and comparative statistics of lipid profile in the H^+S and H^-X haplotypes of LPL gene carriers among studied groups

Lipid Profile	H^+S (n=72) Mean±SD/Median (IQR•)	H^-X (n=20) Mean ±SD/ Median (IQR•)	t/Z*
T.Chol (mg/dL)	181.5 ± 41.1	191.4 ± 27.3	1.006
TG (mg/dL)	120.0 (94.8 – 162.8•)	77.0 (70.0 – 96.5•)	4.270*$^{\Delta}$
HDL-C (mg/dL)	40.5 ± 11.0	51.1 ± 15.1	3.525$^{\Delta}$
LDL-C (mg/dL)	115.0 ± 38.6	123.7 ± 30.4	0.932

LPL: lipoprotein lipase, T. Chol: total cholesterol; TG: triglycerides; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; IQR: interquartile range; SD: standard deviation; Δ:p: <0.05.

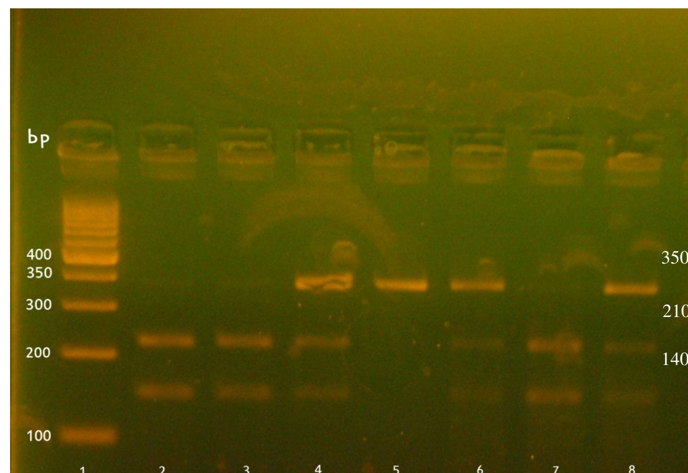

Figure (1): Gel electrophoresis of HindIII polymorphism genotypes. Lane 1: DNA ladder, lanes (2, 3, 7): Homozygous wild (H^+H^+) (210 bp and 140 bp), lanes (4, 6, 8): Heterozygous mutant (H^+H^-) (350 bp, 210 bp and 140 bp), lane 5: Homozygous mutant (H^-H^-) (350 bp).

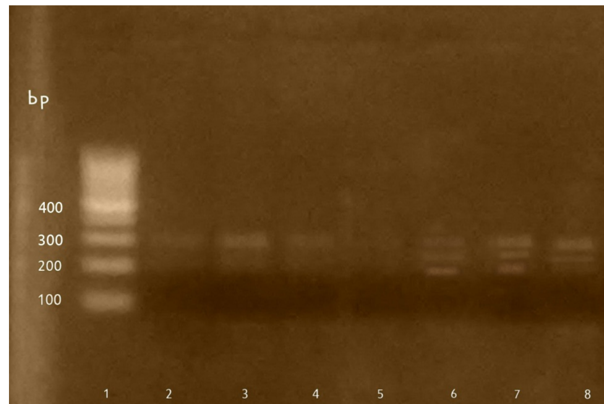

Figure (2): Gel electrophoresis of S447X polymorphism genotypes. Lane 1: DNA ladder, lanes (2, 3, 4): Homozygous wild SS (203 bp and 285 bp), lanes (6, 7, 8): Heterozygous mutant SX (285 bp, 250 bp and 203 bp).

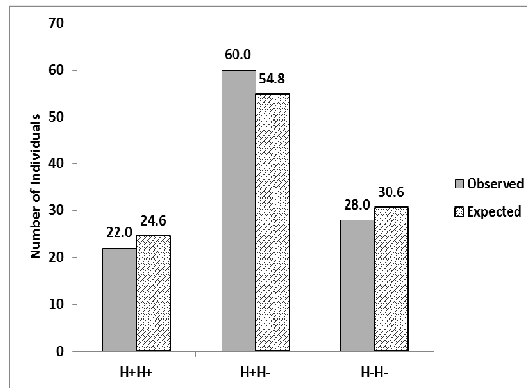

Figure (3): Bar charts showing the comparison between observed and expected genotypes of HindIII and S447X polymorphisms in all studied population.

DISCUSSION

Coronary artery disease is a complex disorder with well- documented genetic and environmental components **(Antonio, 2013).** LPL plays a central role in the metabolism of lipoproteins **(Zambrano et al., 2014).** Nowadays a number of studies started to focus on the influence

of LPL gene mutants on the development of CAD **(Taguturi et al., 2013).**

In the present study, diabetes, hypertension, smoking and hyperlipidemia were selected as CAD risk factors. They were shown to be more frequent in CAD patients than controls. Similar data were reported by **Aggarwal et al. (2012)** and **Rustempasic et al. (2014).**

In the present study, the entire studied population was genotyped for HindIII and S447X LPL gene polymorphisms. The application of Hardy-Weinberg law proved the genetic equilibrium of the studied population as regards the distribution of the studied genotypes. In addition, the genotype and allele frequency of the HindIII polymorphism did not differ significantly between CAD patient and control groups where the former group was less likely to carry the $H^{-}H^{-}$genotype (18.3% vs 34%) and the H^{-} allele (73.3% vs 88%). This finding was in accordance with **Araújo et al. (2010)** and **Daoud et al. (2013).** Regarding the S447X polymorphism, the X allele as well as the SX genotype were statistically more frequent among controls than patients (40% vs 16.7%). These results were confirmed by **Pasalic et al. (2006)** and **Wood et al. (2011),** hence suggesting a protective effect of the X allele against CAD. However, study by **Al-jafari et al. (2012)** disagrees with our findings showing that the S447X polymorphism has no significant association with CAD.

In the present study, the impact of the HindIII polymorphisms on the lipid profile of the included subjects was evaluated. As regards the HindIII polymorphism, the presence of the mutant H- allele did not show any influence on the levels of the different parameters of the lipid profile. Such findings proved that the location of HindIII polymorphism in the middle of intron 8 makes it a non functional polymorphism with almost negligible direct effect on LPL activity **(Antonio et al., 2013; Araújo et al., 2010; Chen et al., 2008).** However, study performed by **Abu-Amero et al. (2003)** on the Saudi population demonstrated strong correlation with CAD. **Antonio (2013)** and **Smith (2006)** attributed such differences between the studies to the hypothesis that LPL-HindIII polymorphism varies across different populations. On the other hand, **Mu˜noz-Barrios et al. (2012)** and **Sagoo et al. (2008)** demonstrated that the HindIII polymorphism is in strong linkage disequilibrium with some LPL

gene variants which they consider the main contributors to the change in LPL activity.

The present study clarified the effect of S447X polymorphism on lipid parameters, where the presence of the X allele was associated with a significantly low level of triglycerides and high level of HDL-C.

Similar data were reported by **Daoud et al. (2013), Turlo et al. (2014)** and **Agirbasli et al. (2011),** where the latter hypothesized that S447X gene polymorphism might have a protective effect for CAD through its favorable effects on lipid levels. The advantageous lipid profile in carriers of the 447X variant is consistent with the increased receptor binding affinity that this 2-amino acid truncation confers on the C-terminal domain, the part of the enzyme important for the LPL-mediated uptake of lipoproteins by receptors on the cell surface **(Sagoo et al., 2008).** Moreover, **Mu˜noz-Barrios et al. (2012)** suggested that the presence of the S allele could be involved in the pathophysiology of cardiovascular disease, due to the availability of FFAs which may affect cardiac function, thus leading to a heart growth as a compensatory effect which increases the risk for cardiovascular disease.

Haplotype reconstruction for the two LPL polymorphisms under study revealed the presence of 72 subjects with H+S haplotype while the haplotype H-X was present in only 20 subjects. H-X haplotype was associated with lower triglyceride levels and higher HDL-C levels when compared to the H+S haplotype. Our results were in accordance with **Araújo et al. (2010)** who highlighted the significant protective effect of the H-X haplotype against CAD.

In conclusion, the present study demonstrated the presence of significant differences in the genotype and allele frequencies of S447X polymorphism of LPL gene in CAD patients as compared to controls being more frequent in the latter group; however, such differences were not detected for the HindIII polymorphism distribution. Carriers of X allele and H-X haplotype had lower triglyceride levels and higher HDL-C levels as compared to those with absent X allele and H+S haplotype. Meanwhile H- allele was not associated with any change in lipid profile. Such finding reflected the protective effect of S447X polymorphism on CAD.

Conflict of interest: The authors declare no conflict of interest.

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الملخص العربي

العلاقة بين تعدد أشكال جين الليبوبروتين ليباز (HindIII , S447X) و مرض الشريان التاجى

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يعتبر مرض الشريان التاجي السبب الرئيسي للاصابات و للوفيات في جميع أنحاء العالم. إن انزيم الليبوبروتين ليباز هو انزيم رئيسي في عملية الأيض للبروتين الدهني. كما يعتبر الجين الخاص بيه جين مرشح كمؤثر فى مرض الشريان التاجي . كان الهدف من هذا العمل هو دراسة العلاقة بين الأشكال المتعددة لجين الليبوبروتين ليباز (HindIII وS447X) و مرض الشريان التاجي وتأثيرها على التمثيل الغذائي للدهون. وقد أجريت الدراسة على ٦٠ مريضا ممن يعانون من مرض الشريان التاجي كما هو محدد من قبل تصوير الأوعية التاجية بالإضافة إلى ٥٠ شخص من الأصحاء بمثابة المجموعة الضابطة. وقد تم الكشف عن تعدد أشكال جين الليبوبروتين ليباز (HindIII وS447X) بأستخدام تقنية تفاعل البلمرة المتسلسل -تقييد جزء طول تعدد الأشكال. وكشفت الدراسة وقوع السكان محل الدراسة في توازن هاردى ونبرج. لم يختلف معدل التعدد الشكلي (HindIII) لجين انزيم الليبوبروتين ليباز بين المرضى والضوابط. في الوقت نفسه كان التعدد الشكلي (S447X) (الطراز العرقى SX و الاليل X) لجين انزيم الليبوبروتين ليباز أكثر تواترا في الضوابط بالمقارنة بمرضى الشريان التاجى. كان لدى حاملي الاليل X و النمط الفردي H^-X مستويات منخفضة من الدهون الثلاثية وارتفاع فى مستويات HDL-C بالمقارنة مع من لديهم الاليل X غائبة و النمط الفرديS^+ H . وفي الوقت نفسه لم تتواجد اي علاقة بين ألاليل $^-$ H و معدل التغيير في مستوى الدهون. وفي الختام، فأن من الممكن اعتبار التعدد الشكلي S447X لجين الليبوبروتين ليباز واحد من العوامل الوقائية ضد تطور مرض الشريان التاجي . وفي الوقت نفسه، فشل التعدد الشكلي HindIII للجين فى اثبات أي صلة مع مرض الشريان التاجي .