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PHARMACOGENOMIC STUDIES OF CHOLESTERYL ESTER TRANSFER PROTEIN (CETP) GENOTYPES IN SUSPECTED CAD PATIENTS

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ABSTRACT: Recent studies have attempted to identify specific genes that contribute to cardiovascular health and disease. Response to various drugs like statins differs from individual to individual, due to polymorphic variations in drug metabolizing genes related to pharmacogenomics of the diseases. The aim of this study was to find out the association of Cholesteryl ester transfer protein (CETP) gene polymorphism rs708272 (Taq1B) with cardiovascular diseases, since variations in the CETP gene alters the HDL-C levels. The study comprises of 100 samples from individuals visiting the hospital for complaints of CVD. The Taq 1 B polymorphism was analyzed by PCR-RFLP method followed by agarose gel electrophoresis. A Taq 1 B polymorphism of CETP gene at intron 1, resulted in C to T transition. This transition induced the variations in the levels of its expression leading to altered phenotypes in the subjects. We found that CT genotypes of CETP gene were associated with higher expression levels as compared to TT and CC genotype. It is concluded that screening of Taq1B polymorphism may help to predict the prognosis of cardiovascular diseases and also their response to statins and other cholesterol lowering drugs.

INTRODUCTION: Coronary artery diseases (CAD), also known as coronary heart disease (CHD), are the number one cause of death in the world and have a high incidence of morbidity and mortality. CAD is a major public health problem in developing and developed countries and its increasing prevalence is a cause of considerable concern in the medical community worldwide [1, 2].

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Each year, the American Heart Association (AHA), in conjunction with the Centers for Disease Control and Prevention, the National Institutes of Health, and other government agencies, brings together the most up-to-date statistics on heart disease, stroke, other vascular diseases, and their risk factors and presents them in its Heart Disease and Stroke Statistical Update.

Coronary heart disease caused ≈1 of every 6 deaths in the United States in 2007. Each year, an estimated 785 000 Americans will have a new coronary attack, and ≈470 000 will have a recurrent attack. It is estimated that an additional 195,000 silent first myocardial infarctions occur each year. Approximately every 25 seconds, an

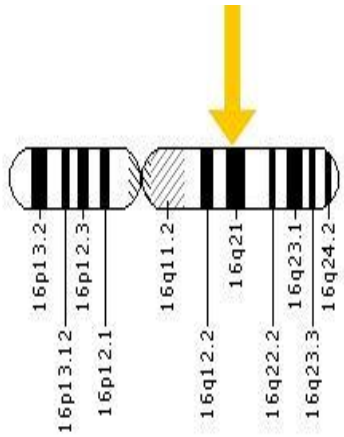
American will have a coronary event, and approximately every minute, someone will die of CVD.

The hypothesis that low high density lipoprotein (HDL) cholesterol concentrations are associated with a greater risk of CHD has been raised since the 1950s [2, 3] and several authors have subsequently proved [4, 5] that HDL cholesterol is also an established independent risk factor for CHD [6]. Further it was also shown to be positively associated with increased CHD risk [7, 8, 9].

CETP shuttles cholesterol-esters from high-density lipoprotein particles (HDL) to low density lipoproteins (LDL). High CETP activity lowers the HDL/total cholesterol ratio, potentially increasing risk for CAD. Therefore, inhibition of CETP offers a new approach to CAD therapy. However, the CETP inhibitor torcetrapib was found to increase cardiovascular events, since HDL increased and LDL decreased substantially [10, 11].

As LDL supports reverse cholesterol transport to the liver, patients with rare genetic defects in CETP present with numerous lipid abnormalities [12]. Recent results further question the validity of the CETP-HDL-CAD relationship under all conditions, showing that low CETP levels can be associated with increased CAD risk [13], possibly because of the functions other than cholesterol transport.

Cholesteryl ester transfer protein (CETP): The CETP gene is located on the long (q) arm of chromosome 16 at position 21. More precisely, the *CETP* gene is located from base pair 56,995,834 to base pair 57,017,755 on chromosome 16.



CETP is a hepatically derived, hydrophobic glycoprotein that binds to HDL. CETP mediates the equimolar exchange of cholesteryl esters from HDL for triglycerides in ApoB lipoproteins (chylomicra, VLDL, and low-density lipoprotein [LDL]). CETP plays an important role in the regulation of HDL metabolism, and the *TaqIB*polymorphism of the CETP gene has been associated with elevated HDL concentrations. The TaqIB, located in intron 1, was suggested to act as a marker for a functional C3A polymorphism in the promoter region of the CETP gene, located 629 base pairs upstream from the transcription start site. This – 629C3A variant has been shown to directly affect CETP promoter activity and, subsequently, HDL concentrations.

Taq1 B polymorphism in CETP: Diverse polymorphisms have been described in the *CETP* gene. The most studied polymorphism is the Taq 1B (rs708272). It is located in the intron 1 of the *CETP* gene and consists of the substitution of a guanine by cytosine, giving rise to the B1 and B2 alleles, respectively. B1 allele is associated with higher CETP activity and thus has lower levels of HDL-C than the B2 allele [14].

In these results, most prominent was the region of CETP containing the rs708272 (Taq1B) polymorphism, previously shown to be strong LD with at least 1 promoter region polymorphism that may influence CETP concentration.

Meta-analysis [REF] has confirmed more than one CETP region polymorphism with an effect on HDL-C level consistent across samples. The presence or absence of a *Taq*I restriction site leads to three possible genotypes for this *Taq*I RFLP: CC, CT, and TT. Individuals with CC (homozygous for the presence of the restriction site) have lower plasma HDL-cholesterol levels, compared to carriers of the T allele.

Pharmacogenomics has the potential to enhance drug efficacy, by allowing patients with the greatest likelihood for benefit to be identified to reduce toxicity by identifying those at greatest toxicity risk. Through pharmacogenomics, it might be possible to identify a priori a drug or drugs most likely to reduce a patient's blood pressure, based on the patient's genetic make-up. While not proven, it seems probable that successful blood

pressure control with the initial drug would increase the patient's likelihood of remaining on their prescribed therapy.

PATIENTS AND METHODS: A group of 100 individuals who visited the hospital were randomly selected to form our study group. Based on the inclusion criteria we selected only those who suspected that they were having chest pain but were not CVD patients. All those who were having other associated diseases were excluded. However we found the some were Diabetic. The project was approved by the Institutional Ethics committee of Mahavir hospital and Research centre.

1. **Sample Collection:** 2ml of blood sample was collected in EDTA vacutainers from these individuals who had come to Mahavir Hospital for master health checkup after obtaining their informed consent. Using a questionnaire we also collected some demographics of all the subjects.

2. **DNA isolation:** Genomic DNA was extracted based on the protocol routinely followed in the lab.

3. **Polymerase Chain Reaction:**

Primers used:

FORWARD PRIMER: 5'-CTGAGCCCAGCCG C ACACTAAC-3'

REVERSE PRIMER: 5'-CACATAGCCCAGA G AGAGGAGTGCC-3'

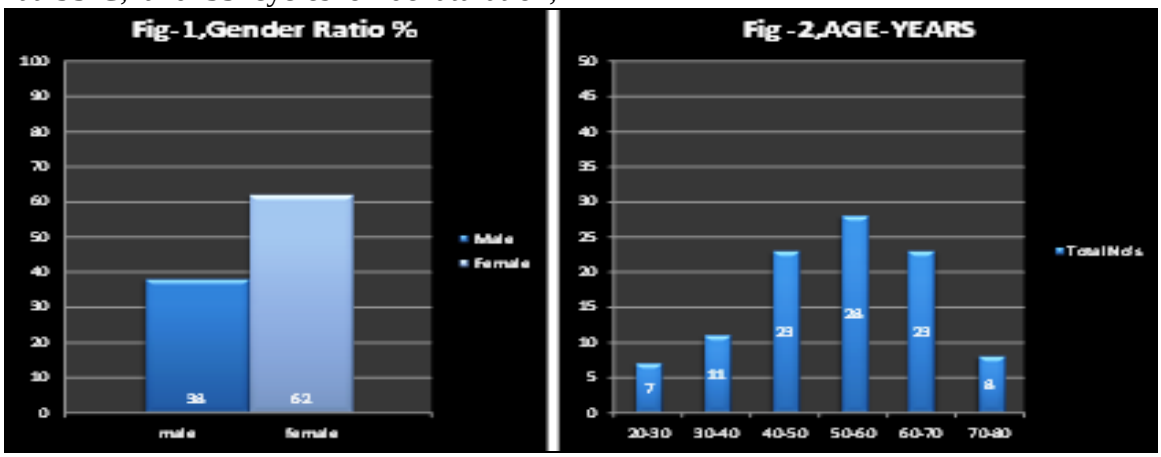
4. **PCR Conditions:** Initial denaturation for 5 min at 95^{o}C, and 35 cycles of denaturation, annealing at 65^{o}C and final extension at 72^{o}C for 5 mins. This was followed by agarose gel electrophoresis to check for amplification.

5. **Restriction Fragment Length Poly-morphism (RFLP):** PCR products were digested using Taq 1 B restriction enzyme 0.1 µL of enzyme was added to 15 µL of PCR product and incubated at 37°C for 16 hours. Then it was run through 2% agarose gel at 90V for 30mins, and visualized in gel documentation system to identify the genotypes. The restriction digestion of PCR product yielded three different patterns.

These RFLP products were 174 bp and 354 bp (CC genotypes-2 bands), 528 bp, 354 bp and 174bp (CT genotypes -3 bands) and 528 bp (TT genotype, single band) (Shown in figure-6).

RESULTS: The demographics of the subjects included in this study were collected using a questionnaire, are presented in these **figures 1, 2 & 3** below:

There were more females in this study as compared to males (Figure 1). Hence, it may be possible that females appeared to be more prone to the diseases than males. Females were mostly either housewives or retired personnel stayed at home, it can be possible that stress factor or overeating could have induced the disease. The susceptible age group of this disease was found to be between 40-70 years of age Figure 2. CAD mostly affects the age group of > 50 years. Further we also found that 39% were diabetic Figure 3.



THE DEMOGRAPHICS OF THE SUBJECTS INCLUDED IN THE STUDY

FIGURES 1 & 2: DEMOGRAPHICS OF THE SUBJECTS INCLUDED IN THIS STUDY- GENDER WISE AND AGE DISTRIBUTION

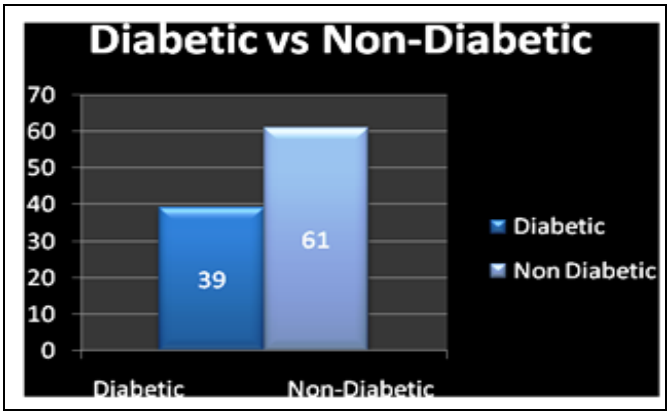


FIGURE 3: SHOWING THE SUBJECTS WITH DIABETIC CONDITIONS, DIABETES WAS MORE IN FEMALES THAN IN MALES

Genomic studies: DNA extracted from the blood samples was checked for the quality and quantity using 'Nanodrop' and also checked on 1% agarose gel. After checking for the purity of DNA, PCR was performed using the primers (mentioned in materials and methods), as shown in **figure 4**.

Genotyping of CETP Taq1B (C/T) polymorphism:

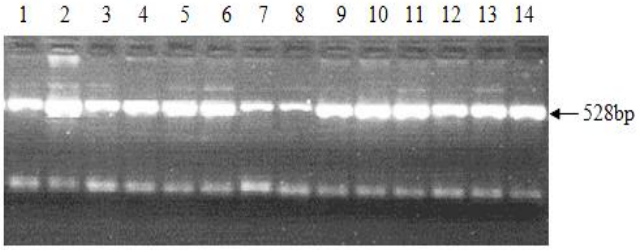


FIGURE 4: ETHIDIUM BROMIDE STAINED 2% AGAROSE GEL PICTURE SHOWING PCR PRODUCT BANDS

RFLP studies: Upon digestion with TaqI, an uncut PCR product of 528bp fragment indicate TT genotype, while 354 and 174 bp fragments indicated homozygous CC geneotype and CT heterozygous had 528,354 and 174 bp fragments when visualized on 2% agarose gel stained with EtBr, as shown in **Figure 5**.

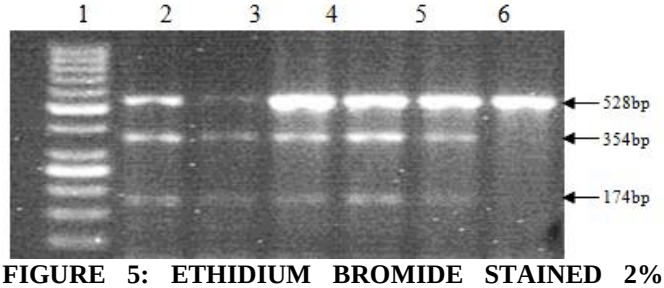


FIGURE 5: ETHIDIUM BROMIDE STAINED 2% AGAROSE GEL PICTURE SHOWING RFLP PRODUCTS

Out of a total of 100 individuals which were genotyped, CT genotype was found in 72% and TT genotype was found in 21% and CC genotype was found in 7% as shown in **Figure 6**.

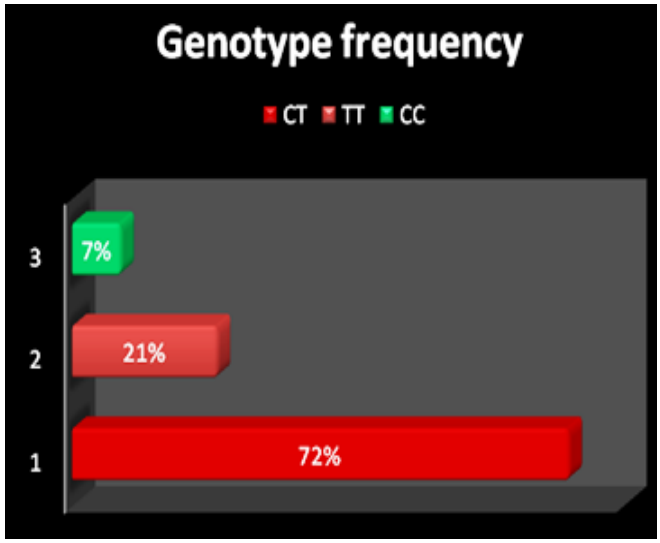


FIGURE 6: GENOTYPE FREQUENCY OF PATIENTS

Lipid profiling of the study group: To determine the relationship between Taq1B polymorphism and lipid levels, lipids and CETP activity were measured in subjects, with and without Taq1B polymorphism.

Mostly the two forms of cholesterol that are diagnosed are Low-density lipoprotein (LDL) and high-density lipoprotein (HDL). These have opposite actions, LDL is the main source of artery-clogging plaque and HDL works to clear cholesterol from the blood.

Triglycerides are another fat in the bloodstream; research has shown that high levels of triglycerides may also be linked to heart disease.

The diagnosis for cardiovascular disease includes all these parameters which are reported below (**Table 1**) for healthy individuals and denoting the desirable levels since any deviations from this desirable levels may lead to the disease condition.

TABLE 1: SHOWING REFERENCE LEVELS OF HDL, LDL, TOTAL CHOLESTEROL AND TRIGLYCERIDES

HDL	
>60 (mg/dL)	Desirable - helps to lower risk of heart disease
<40(mg/dL)	Major risk factor -- increases the risk for developing heart disease

LDL Cholesterol	
Less than 100(mg/dL)	Optimal
100 – 129(mg/dL)	above optimal
130 – 159(mg/dL)	Borderline high
160 – 189(mg/dL)	High
190 and above(mg/dL)	Very high
Total Cholesterol	
Less than 200(mg/dL)	Desirable
200 – 239(mg/dL)	Borderline High
240 and above(mg/dL)	High
Triglycerides	
Below 150(mg/dL)	Desirable
150-199(mg/dL)	Borderline high
200-499(mg/dL)	High
500(mg/dL) and above	Very High

Human plasma contains cholesteryl ester transfer protein (CETP) which, besides other functions, enables the transfer of cholesteryl esters in plasma from high-density lipoproteins (HDL) towards triglyceride-rich lipoproteins, thereby contributing to lower HDL cholesterol.

Variations in the CETP gene, including the intronic TaqIB polymorphism (rs708272), are common in the population.

DISCUSSION: In this study, we evaluated a common CETP Taq 1 B polymorphism (rs708272), which is reportedly a proatherosclerotic SNP of the candidate gene. CETP gene polymorphism is known to be associated with changes in lipid profiles.

Primary hyperlipidaemia is considered to be a major risk factor for pancreatitis, atherosclerosis and coronary heart disease. This is a risk factor diagnostic which can be used as a tool to identify individuals at risk of developing cardiovascular disease [15].

The CETP gene is polymorphic and many genetic variations have been identified in both coding and non-coding regions. Various polymorphisms associated with CETP have been studied; among them Taq 1 B is the most widely studied. The Table below depicts the world statistics of CETP gene Taq 1B polymorphisms (**Table 2**).

Some study reports [16] that among the nine polymorphisms only CETPrs708272/TaqIB was able to discriminate between symptomatic and asymptomatic patients.

TABLE 2: GENOTYPE FREQUENCIES OF CETP GENE Taq 1 B POLYMORPHISM IN VARIOUS POPULATIONS OF THE WORLD

Population	CC (%)	CT (%)	TT (%)	Reference no.
Amsterdam	32	49	19	17
Finland	32	49	19	18
Japan	38	41	21	19
Saudi Arabia	32	46	22	20
China	32.2	51	16.8	21
USA, (Caucasians)	33	45	22	22
Mumbai, India	27	46	27	23

Frequency of CT genotype varies worldwide as shown in the above table 2. The frequency of homozygous TT was also higher .It also supports that the frequencies of T allele/TT genotypes are higher in Indians than in other populations. Studies in these populations show enormous variations in the frequency of the genotypes; this may be due to different ethnic groups studied (as shown in the table 2).

The presence or absence of a *Taq*I restriction site leads to three possible genotypes for this *Taq*I RFLP: CC, CT, and TT. Individuals with CC (homozygous for the presence of the restriction site) have lower plasma HDL-cholesterol levels, compared to carriers of the T allele.

Pharmacogenomics has the potential to enhance drug efficacy, by allowing patients with the greatest likelihood for benefit to be identified and to reduce toxicity by identifying those at greatest toxicity risk [24].

Through pharmacogenomics, it might be possible to identify a priori a drug or drugs most likely to reduce a patient's blood pressure, based on the patient's genetic make-up. While not proven, it seems probable that successful blood pressure control with the initial drug would increase the patient's likelihood of remaining on their prescribed therapy.

In India, there is a heterogeneous population and it would be desirable to find out the gene frequency and lipid profile in sub-populations of the country. Early establishment of population at risk and control of high-risk environmental factors should be helpful in lowering the burden of disorders associated with dyslipidaemia.

The present study is limited by the small sample size however, despite these limitations it may contribute to novel aspects to the important field of personalized medicine. A molecular diagnostic test is particularly if the risk allele frequency is high and the pathogenic impact of the polymorphism is reasonably strong in the population.

To date, not many genetic tests for complex polygenic disorders have been evaluated by such an approach, taking into account the impact that CETP rs708272C which may have on the incidence of cardiovascular events in the individuals. Several studies have reported association of Taq I B polymorphism with lipid variation; T allele has been shown to be associated with higher HDL-cholesterol levels.

Considering that CETP deficiency is the main cause of high HDL-cholesterol in some populations, there must be some other genetic variants of the CETP gene also contribute in lipid variation.

Statins exhibit action beyond lipid-lowering activity in the prevention of atherosclerosis. Researchers hypothesize that statins prevent cardiovascular disease via four proposed mechanisms;

(i) Improve endothelial function

(ii) Modulate inflammatory responses

(iii) Maintain plaque stability and

(iv) Prevent thrombus formation.

Variability in response to statin therapy results from environmental and non-genetic factors, such as age, gender, diet, smoking status, and physical activity [25]. Just as inter-individual variability in plasma lipid and lipoprotein levels is governed by hereditary factors, it stands to reason that statin-response of these same parameters is also related to genetic heterogeneity.

Genetic variation can contribute to inter-individual variations in clinical efficacy of drug therapy, and significant progress has been made in identifying common genetic polymorphisms that influence responsiveness to Statin therapy.

In the present study, the genotypic frequencies for CT genotype, TT genotype and CC genotype were obtained as 72%, 21% and 7% respectively. CETP rs708272 C allele may become an essential part of algorithms developed to predict an active, symptomatic course of atherosclerosis, as shown in **Table 3**.

TABLE 3: GENOTYPE FREQUENCIES OF CETP GENE TAQ 1 B POLYMORPHISM IN OUR STUDY

Population	CC%	CT%	TT%
Hyderabad (India)	7%	72%	21%

Genetic testing has several advantages over plasma biomarker assessment:

a) DNA tests can be performed under lipid lowering therapy which may influence lipoprotein levels,

b) Testing has to be performed once in a lifetime and not repetitively and

c) SNPs affecting the functional activity of an enzyme or protein that is not accessible in the plasma compartment may reflect functional state more accurately than plasma levels of substrates.

CONCLUSION: Cholesteryl ester transfer protein (CETP) is a major determinant of plasma lipid and lipoprotein levels. Genetic polymorphisms were determined by PCR-based detection method and the results showed that Taq 1B polymorphism of CETP gene was associated with variations in lipids profile in the selected population and might have a role in contributing to genetic risk of developing coronary artery disease.

Further, our results also suggest that Taq IB polymorphisms in CETP gene were also associated with healthy control subjects to some extent in this cohort. It is of interest that this SNP rs708272 is most significantly associated with CVD- mostly myocardial infarction; this SNP defines the B2 allele of the *CETP* TaqIB polymorphism and also as the core candidate *CETP* SNP in the recent comprehensive meta-analysis. Hence, we believe that genotyping of this SNP improves the power of diagnosis and could serve as an excellent biomarker for molecular medicine.

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Conflict of Interest: None Declared.

REFERENCES:

1. He, J., Gu D, Wu X, Reynolds K, Duan X, Yao C, Wang J, Chen CS, Chen J, Wildman RP et al. Major causes of death among men and women in China. N Engl J Med. 2005; 353: 1124-1134.
2. Anetta LB, Przemysław P, Zofia K. Elevated factor VIII level and stroke in patients without traditional risk factors associated with cardiovascular diseases. Neuropsychiatr Dis Treat. 2013; 9:847-852.
3. Barr DP, Russ EM, Eder HA. Protein-lipid relationships in human plasma. Am J Med. 2005; 11: 480-5.
4. Castelli WP, Garrison RJ, Wilson PW, Abbott RD, Kalousdian S, Kannel WB. Incidence of coronary heart disease and lipoprotein cholesterol levels. The Framingham Study. JAMA. 1986; 256: 2835-8.
5. Yaari S, Goldbourt, Even-Zohar S, Neufeld HN. Associations of serum high density lipoprotein and total cholesterol with total, car- diovascular, and cancer mortality in a 7-year prospective study of 10000 men. Lancet. 1981; 1: 1011-5.
6. Packard C, Saito Y. Non-HDL cholesterol as a measure of atheroscle-rotic risk. J Atheroscler Thromb. 2004; 11: 6-14.
7. Nagano M, Yamashita S, Hirano K, et al. Molecular mechanisms of cholesteryl ester transfer protein deficiency in Japanese. J Atheroscler Thromb. 2004; 11: 110-21.
8. Qi YU, En-qi LIU, Si-hai ZHAO, Ya-feng LI, Yan-li WANG, Yu-long CHEN, Bing-qiao HUANG, Jian-lin FAN, Peng-hui YANG. Association between TaqIB polymorphism of cholesteryl ester transfer protein and coronary artery disease in the Chinese population. J Zhejiang Univ-Sci B (Biomed & Biotechnol) *2012*; 13(5):342-347.
9. Yongjian Lu,Naeimeh Tayebi,Hongzhe Li ,Nilmani Saha ,Hongyuan Yang ,Chew-Kiat Heng . Association of CETP Taq1B and -629C > A polymorphisms with coronary artery disease and lipid levels in the multi-ethnic Singaporean population. Lipids in Health and Disease .2013; 12:85 doi: 10.1186/1476-511X-12-85.
10. Barter PJ: Coronary plaque regression: role of low density lipoproteinapheresis. J Am Coll Cardiol. 2002; 40:228–30.
11. Cameron JD, Asmar R, Struijker-Boudier H, Shirai K, Sirenko Y, Kotovskaya Y, Topouchian J. Current and future initiatives for vascular health management in clinical practice.Vasc Health Risk Manag. 2013; 9:255-64.
12. Zhong S, Sharp DS, Grove JS, Bruce C, Yano K, Curb JD, Tall AR. Increased coronary heart disease in Japanese-American men with mutation in the cholesteryl ester transfer protein gene despite increased HDL levels. J Clin Invest. 1996; 15; 97(12):2917-23.
13. Vasan RS, Pencina MJ, Robins SJ, Zachariah JP, Kaur G, D'Agostino RB, Ordovas JM. Association of circulating cholesteryl ester transfer protein activity with incidence of cardiovascular disease in the community. Circulation. 2009; 15; 120(24):2414-20.
14. L. Lopez Rios, P. Perez Jiemenez ,E. Martinez Quitanad, G. Rodriguez Gonalezeb, B.N. Diaz Chicob, F.J. Novoaae,L.Serra Majemc,R.Chirinob. Association of Taq 1B CETP polymorphism with insulin and HOMA levels in the population of the Canary Islands. 2011.
15. Zdrojewski T, Rutkowski M, Bandosz P, Gaciong Z, Jędrzejczyk T, Solnica B, Pencina M, Drygas W, Wojtyniak B, Grodzicki T, Piwoński J, Wyrzykowski B. Prevalence and control of cardiovascular risk factors in Poland. Assumptions and objectives of the NATPOL.Survey.Kardiol Pol. 2013; 71(4):381-92. doi: 10.5603/KP.2013.0066.
16. Priska Erzberger, Marie-Theres Gomberta, Marcus Mutschelknauss, Moritz Wyler von Ballmoos, Barbara C. Biedermanna. A CETP polymorphism improves the diagnostic power of clinical examination in patients with cardiovascular disease. SWISS MED WKLY. 2011; 140(21–22):307–313·
17. Kuivenhoven, J. A. *et al*., Heterogeneity at the CETP gene locus: Influence on plasma CETP concentrations and HDL cholesterollevels. Arterioscler. Thromb. Vasc. Biol. 1997; 17, 560–568.
18. Kauma, H., Savolainen, M. J., Heikkila, R., Rantala, A. O., Lilja,M., Reunanen, A. and Kesaniemi, Y. A., Sex difference in the regulation of plasma high density lipoprotein cholesterol by genetic and environmental factors. Hum. Genet. 1996; 97, 156–162.
19. Meguro, S. *et al*., Cholesteryl ester transfer protein polymorphism associated with macroangiopathy in Japanese patients with type-2 diabetes. Atherosclerosis. 2000; 156, 151–156.
20. Al-Daghri, N. M. *et al*. Association between the cholesteryl ester transfer protein TaqI-detectable B polymorphism and low high density lipoprotein cholesterol concentration in Saudis. Clin.Sci. (London). 2003; 105,467–72.
21. Hsu, L. A., Ko, Y. L., Hsu, K. H., Ko, Y. H. and Lee, Y. S., Genetic variations in the cholesteryl ester transfer protein gene and high density lipoprotein cholesterol levels in Taiwanese Chinese. Hum.Genet., 2002; 110, 57–63..
22. Cuchel, M., Wolfe, M. L., deLemos, A. S. and Rader, D. J., The frequency of the cholesteryl ester transfer protein-TaqI B2 allele is lower in African-Americans than in Caucasians. Atherosclerosis.
23. Mukherjee, M. and Shetty, K. R., Variation in high density lipoprotein cholesterol in relation to physical activity and TaqI B polymorphism of the cholesteryl ester transfer protein gene. Clin.Genet. 2004; 65, 412–418.
24. Alizadehsani R, Habibi J, Bahadorian B, Mashayekhi H, Ghandeharioun A, Boghrati R, Sani ZA. Diagnosis of coronary arteries stenosis using data mining.J Med Signals Sens. 2012; 2(3):153-9.
25. Booth FW, Roberts CK, Laye MJ. Lack of exercise is a major cause of chronic diseases. Compr Physiol. 2012 Apr 1; 2(2):1143-211. doi: 10.1002/cphy.c110025.

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