

Association of Apolipoprotein E Gene Polymorphism with Lipid Profile in Patients with Acute Coronary Syndrome in Han Chinese: A Critical Review

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How to cite this paper: Nawabi, A.Q., Yang, M.M., Cai, X.M., Gou, W.J., Hou, J.T., Nizami, V. and Dai, Q.M. (2019) Association of Apolipoprotein E Gene Polymorphism with Lipid Profile in Patients with Acute Coronary Syndrome in Han Chinese: A Critical Review. *World Journal of Cardiovascular Diseases*, 9, 825-845. <https://doi.org/10.4236/wjcd.2019.911074>

Received: May 24, 2019

Accepted: November 17, 2019

Published: November 20, 2019

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Abstract

This review paper focuses on the genetic contribution, in particular, the association of Apolipoprotein E gene polymorphism to lipid abnormality and subsequent acute coronary syndrome in Han Chinese of China. Many researches have been published pertaining the influence of ApoE gene polymorphism on coronary artery disease, dyslipidemia and the response of statin in Han Chinese. Most of the studies in Han Chinese like other populations demonstrated that ApoE 4 allele genetically predisposes coronary artery disease, acute coronary syndrome, severity of occlusion of coronary artery and higher incidence of major adverse cardiovascular events (In Han Chinese, ApoE allele carriers demonstrated 85% increase in major adverse cardiovascular events (MACE) in six months follow up). In addition, ApoE4 allele carrier also showed both increased in LDL level and decrease response to statin therapy in dyslipidemic Han Chinese. On the other hand, ApoE2 carrier is scavenger of cholesterol and triglyceride from the blood; thus it is cardiovascular-protective. Despite positive relationship between ApoE gene polymorphism and cardiovascular pathologies, prognostic outcome and resistance to intervention, this area of research still requires extensive investigation in Han Chinese. Because, several other studies revealed either negative effect or showed no effect by ApoE gene polymorphism on cardiovascular disease. Some of the causes of such debatable results could be explained by factors such as diminutive frequency allele and expression of ApoE gene in coronary heart disease. This part of the research yet requires extensive study with bulkier sample size and retrospective in nature, in order to ascertain the influ-

ence of ApoE genotype on lipid, anti-hyperlipidemic agent and coronary heart disease. Such studies could assist us to confirm whether to test healthier subjects to predict genetic risk of coronary heart disease in Han Chinese population. The aim of this review paper is to critically analyze the effect of ApoE gene on the occurrence of coronary heart disease in Han Chinese.

Keywords

Apolipoprotein E Gene Polymorphism, Acute Coronary Syndrome, Dyslipidemia, Han Chinese

1. Introduction

Among adult cardiovascular mortality in China, Coronary Artery Disease stands as 2nd prominent cause [1] [2]. Although the prevalence of Coronary Artery Disease keeps rising in China, its prevalence is comparatively low to western countries. The data released in 2015 by China Health and Family Planning Commission's Statistical yearbook demonstrated that the death rate from CAD has drastically ascended in China as shown in **Figure 1** [3]. There is a continuous tendency of increased mortality and morbidity from Coronary Artery Disease in urban and rural areas. However, it is dramatically greater in metropolitan areas than country areas. Some of the factors of higher mortality and morbidity caused by urbanization are unhealthy life style and increased number of old age population [4].

Presently, the most common etiology of both mortality and morbidity in China, is led by acute coronary syndrome, which has approximately reached 2.8 million Syndrome patients in China [1]. The rapid transition in life style in China and concomitant intensification in major risk factors have resulted in high incidence of ACS admissions in hospitals as shown in **Figure 2** [5], as it can be observed in the figure that morbidity and mortality in both urban and rural areas have drastically augmented.

Coronary Artery Disease is a poly-factorial sickness, which includes psychological factors, socioeconomic status, life style and genetic factors. Classical risk factors such as diabetes mellitus, HTN, dyslipidemia and smoking account for 85 to 90 percent of coronary heart disease [5] [6].

On the contrary, there are 10% to 15% patients who don't carry classical risk factors, and however, get coronary heart Disease. Some of them could be attributed to genetic cause, in particular premature Coronary Artery Disease which could be related to genetic component. We need to concentrate on newer factors in order to be able to forecast the future risk and determine timely intervention in addition to the conventional risk factors as genetic factors, in particular gene polymorphism [7].

The knowledge of genes affecting cardiovascular diseases, is very limited. Most of the cardiovascular diseases are polygenetic. We know little about cardiovascular

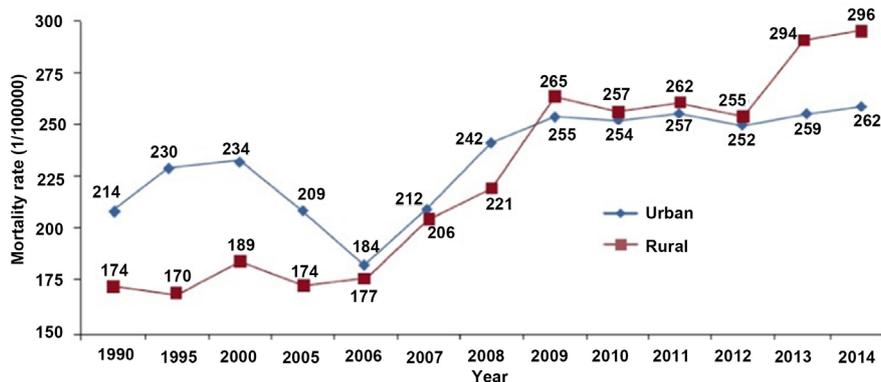


Figure 1. Coronary heart disease mortality tendency in city and country-areas in China: 2002-2014. Exported from Wei-Wei CHEN, *et al.* [1].

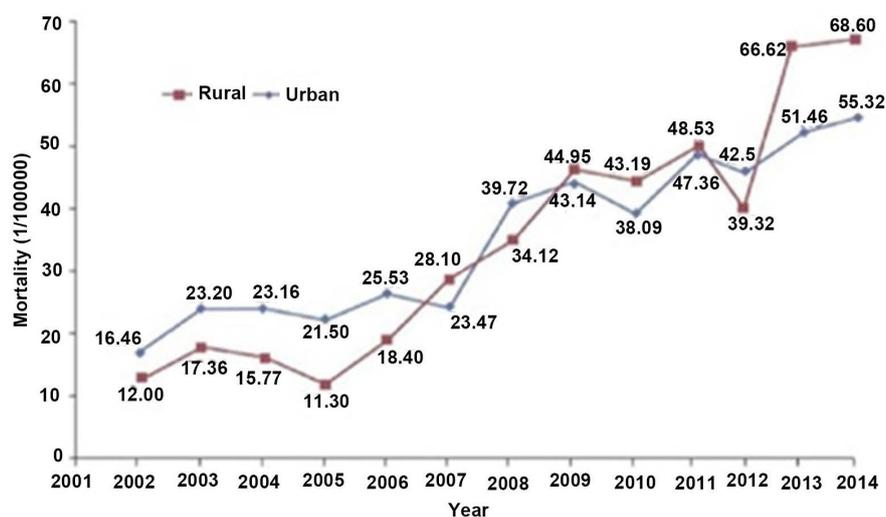


Figure 2. AMI mortality tendency in urban and rural regions in China: 2002-2014. Exported from Wei-Wei CHEN, *et al.* [1].

disorders which are single-gene Mendelian pattern. Examples of such disorders are familial hypercholesterolemia, long QT syndrome and hypertrophic cardiomyopathy [8].

Familial hypercholesterolemia which is a single gene lipid disorder, can cause hyperlipidemia and subsequent premature Coronary Heart Disease [9]. Apolipoprotein E gene is a highly investigated and the most intriguing gene, which is polymorphic in different ethnic groups; however there isn't any confirmed clinical implication.

The impending genetic threatening factor, is ApoE gene polymorphism for coronary artery disease and acute coronary syndrome. Structurally, human ApoE is a glycoprotein, made up of 299 amino acids, found as an important component of different lipoprotein such as HDL, intermediate density lipoprotein, very low density lipoprotein and chylomicrons L. It works as a ligand to help in the uptake of lipid and bind to the respective receptor, thus scavenging lipid from the serum [10].

ApoE protein, is the product of the ApoE gene which is situated on chromosome 19q 13.2, consists of three introns and four exons [11] [12]. It consists of 3597 nucleotides. ApoE polymorphism has three different isoforms which are ApoE2, ApoE3 and ApoE4, synthesizing six various alleles such as E2/E2 (counted as E2 or E2 homozygous), E2/E3 (counted as E2 or E2 carrier), E3/E3 (counted as E3 and is the most common isoform amongst all three isoforms), E2/E4, E3/E4 (counted as E4 carrier), and E4/E4 (E4 homozygous) [13].

Since ApoE genotype polymorphism was first defined in patients who had dysbetalipoproteinemia and the effect of ApoE gene polymorphism that is why multiple studies were piloted to find the influence of lipid and subsequently cause coronary artery disease in various racial group. Since it is polymorphic in nature, which means there is variation amongst the expression of particular isoform, thus different prevalence of cardiovascular diseases in different ethnicities.

The polymorphic nature of the gene explains the mechanism by which altered phenotype changes the lipid metabolism, thus either leading the pathway for atherosclerosis or protecting against it [8] [14]. In most of reports amongst different populations, it has been documented that ApoE4 isoform predisposes to genetically higher risk of acquiring coronary heart disease and acute coronary syndrome while ApoE2 carrier has a negative linkage with CHD. In addition, people who have longer life time, are carrier of ApoE genotype.

Song *y et al.* reported the first meta-analysis on this particular gene polymorphism and ischemic heart disease, the result was expected as ApoE allele, with greater chance of acquiring IHD in contrast to E3 homozygous patients. In similar study, it was reported E2 carrier had no impact on ischemic heart disease (OR, 0.98 [CrI, 0.66 to 1.46] [15]). Nevertheless, different factors were not considered into account such as variation in topography, gender, allele frequency in dissimilar populations, which made is less reliable. In addition, since the frequency of genotype varies from population to population, ApoE gene from various ethnic groups cannot be meta-analyzed. For example, a study performed in Afro-Caribbeans did not show any high difference in Acute Coronary Syndrome and ApoE E genotype. However, it did show that ApoE4 had hyperlipidemia [16]. This contrasts with other studies both in Han Chinese and other racial groups, which show a positive relationship with ApoE4 and Coronary Artery Disease.

In contrast to other Asians such as Japanese (10.5%), Korean (9%), Thai (12.54%), Malaysian, and other ethnicities, Han Chinese (7.5%) makes the lowest frequency of ApoE4 in Asia [17]. Because of the genetic difference in ApoE E gene, recently, several basic researches and cross-sectional researches have been engrossed on the impact of ApoE gene polymorphism and ischemic heart disease amongst Han Chinese. However, the results have been inconsistent and many studies have been published in Chinese language. In addition the samples of most the studies are small and cross-sectional. Therefore a study with adequate sample size is required. This review would focus on the relationship of ApoE gene polymorphism on Coronary Artery Disease in Han Chinese, specially, Acute Coronary Syndrome, the effect of statins in different alleles of ApoE

polymorphism and the mechanism of ApoE gene impacting as a genetic risk factor in the pathophysiology of ischemic heart disease.

2. Apolipoprotein E Isoform and Its Influence on Lipid Metabolism

ApoE was for the first time known in patients with dysbetalipoproteinemia and its contribution in lipid metabolism is one of the highly postulated mechanisms causing dyslipidemia and secondarily leading to Coronary Artery Disease.

In order to understand the effect of Apolipoprotein isoform on lipid metabolism, one must know the normal morphology of ApoE phenotypes and its interaction with the receptor. Studies have been published which have shown that some of the isoforms of Apolipoprotein E are related to cardiovascular diseases while others are protective. It solely depends which isoform is present in a subject type of ApoE isoform.

2.1. Structure of Apolipoprotein Isoform

As shown in **Figure 3** Apolipoprotein E protein is made up of two peculiar anatomical and functional parts which are hinged by consisting of two eccentrically structural and functional domains that are interlocked by an enzyme sensitive protease-sensitive coil [18]. The carboxyl-terminal domain contains sites for both lipid and heparin [18] [19]. These sites physiologically on c-term are believed to perform a vital role, by facilitating the collaboration between the lipid particles and cell-surface heparin sulfate proteoglycans on the vascular wall, augmenting the catalytic function of LPL leading to hydrolysis of these lipid particles [19].

On the other hand, NH₂ end of the protein is supposed to bind to the various receptors. ApoE performs as a ligand for multiple hepatic receptor in order to clear metabolic remnants of Apolipoprotein B-containing lipoprotein, particularly chylomicrons and VLDL, which traffic triglycerides from the intestine and liver to the peripheral tissue respectively [18]. The receptors which bind to NH₂ terminus of the ApoE are VLDL receptor, LDL receptor and LDL receptor-related proteins through heparin sulfate proteoglycan (HSPG) [21] [22] (**Figure 4**).

2.2. Dispersal of ApoE on Lipoproteins

The lipoprotein pathway and the involvement of Apolipoprotein E has been demonstrated in **Figure 5**. There is no ApoE isoform present on IDL and LDL lipoprotein in pre-prandial state but found on VLDL and HDL. After food intake, the residues of chylomicrons like that of VLDL are sequestered swiftly. Both the ApoCii and ApoE are present in 50% of the VLDL [23]. The co-existence of ApoE with ApoCii, makes the clearance of lipid stalled which is facilitated via ApoE. The lipo B-holding lipoprotein comprising ApoE which contain ApoE doubles in quantity in 4 to 5 hours post-prandially, and slowly regresses to LDL after six to 7 hours and at 10 hours completely vanishes [24].

The synthesis of HDL is started by ApoE with the help of ABCA1 transporter by transporting cholesterol and phospholipid from the ABCA1 transporter,

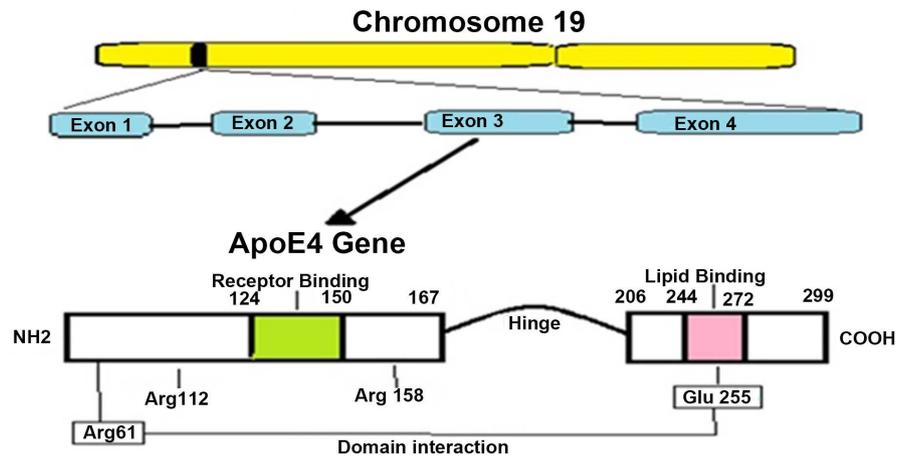


Figure 3. Showing the structure of Apolipoprotein E (The figure has been modified from “Localization of genes encoding apolipoproteins CI, CII, and E to the p 13-cen region of human chromosome 19. Scott J, Knott TJ, Shaw DJ, Brook JD” [11]).

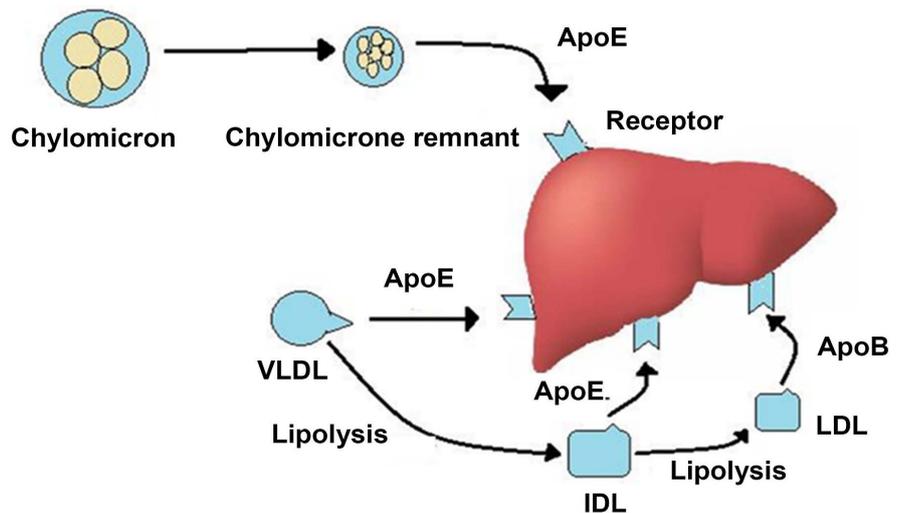


Figure 4. Shows the lipoprotein metabolism facilitated by diet derived chylomicrons and lipoprotein produced in the liver, VLDL are hydrolyzed in the circulation by lipoprotein lipase. Plasma lipoprotein metabolism mediated by ApoE. The residuals of chylomicron and remnants of VLDL can be cleared from the plasma with the help of liver, which has receptors for LDL or the HSPG/LRP pathway. Eventually, thoroughly hydrolyzed LDL have consumed the ApoE ligands and can merely the uptake of the LDL can be via Apo-lipoprotein b (the figure is modified from Division of Translational Medicine and Human Genetics, Perelman School of Medicine at the University of Pennsylvania, 11 - 130 Translational Research Center, Philadelphia, PA, USA [20]).

however, there is variation in effective function in the isoform of ApoE. For example ApoE3 is a better synthesizer of HDL than ApoE4. The efficiency of ApoE4 is upgraded by peptide CS 6253 [25].

2.3. Effect of ApoE Isoforms on Lipoprotein

It has been shown that different isoforms of ApoE have different effect on different Apolipoprotein. For instance, it was revealed by M S Weintraub *et al.* that

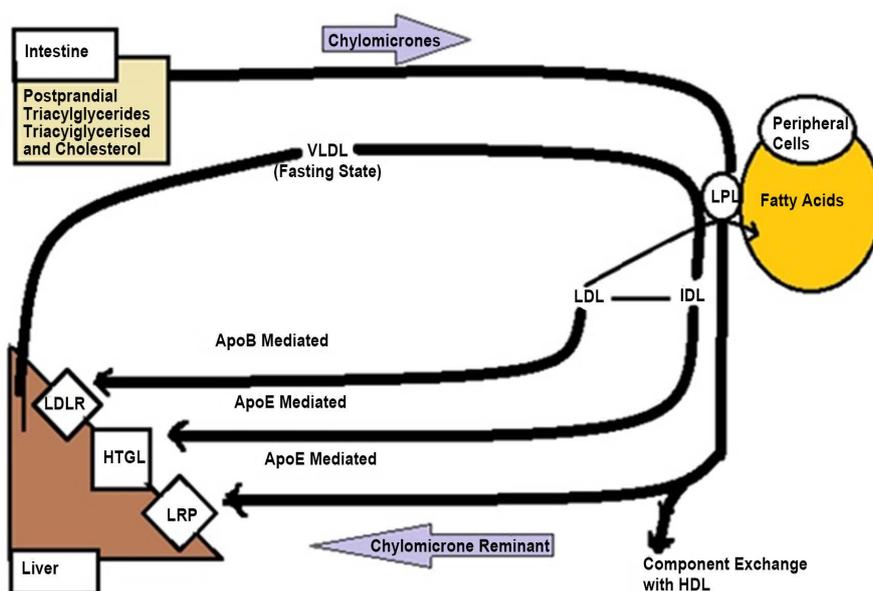


Figure 5. The lipoprotein pathway, metabolism and the involvement of Apolipoprotein E.

the clearance of chylomicron was delayed by ApoE2 isoform while was speedy with ApoE3 and ApoE4 isoforms [26]. In a similar manner, it was also demonstrated that ApoE genotype had noticeable influence on ApoE genotype attached to VLDL but null effect on the free plasma ApoE isoforms. ApoE protein is discovered in different sequences on VLDL particles, however, it is at low amount in people with ApoE4, which is explains increased clearance [27].

ApoE isoform mostly influence LDL and apolipoprotein B plasma concentration in fasting state. The effect also depends on sex and premenopausal and postmenopausal state of females, which clearly shows hormonal influence. For example in male, ApoE2 decreased LDL cholesterol by 0.24 mmol/L while in female subjects, it was between 0.21 mmol/L to 0.53 mmol/L depending on premenopausal and postmenopausal state, respectively [28]. On one hand, ApoE isoform is not present on LDL, on the other hand it affects the size and the plasma quantity of LDL.

It is known that minute LDL is associated with ischemic heart disease and decrease level of HDL. There are many researches which have shown that ApoE isoform have various effect on LDL and HDL, however, both methodology and participants were different. ApoE2 carrier showed minute LDL particle while no effect on the size of HDL particle, on the other hand, ApoE4 carrier showed smaller size of HDL particle but no effect on LDL particle size [29]. A study conducted in intermediate aged Curation patients , showed ApoE2 carrier had effect on the size of LDL particle in male while no effect in female [30].

Another study in Kuwaiti Arabs reported that there was no difference on LDL particle size between ApoE2 carrier and non-ApoE2 healthy subjects. However, elderly subjects carrying ApoE2 with coronary artery disease had smaller particle

of LDL [31].

ApoE protein found on the subset of Apolipoprotein A. In lipoprotein, which have ApoE in its structure, should also consist Apo(A) and Apo(B) in minute size almost like LDL as in contrast to the found on VLDL. Lipoprotein (A) which is of two types, which is classified based on the presence and absence of ApoE. Bach-Ngohou K *et al.* in normal lipid profile subjects showed almost 16.2% ApoE [Lp(a):B:E] and high triglyceride. In this study, ApoE did not have any direct effect on ApoE [Lp(a):B:E]. However, ApoE attached to [Lp(a):B:E] plays an important role in the concentration of lipoprotein a subtype and subsequently triglyceride-dominant particles [32].

ApoE gene polymorphism affects the Apolipoprotein A clearance and plasma concentration. For example, ApoE2/E2 genotype has 65% less concentration of Apo(A) than ApoE4/E4 genotype [33]. In addition, elevated plasma concentration of Apo(A) also showed elevated LDL amount which is well-matched to familial hypercholesterolemia (concluding that there is little activity at the LDL receptor level). E2/E2 did not have too much effect on Apo(A) plasma amount as it was anticipated. However, it augmented the increment of Apo(A) in subjects with compromised plasma clearance of LDL. ApoE2 genotype is a very robust factor in determining the low concentration of Apo(A). Nevertheless, it did not alter the relationship of Coronary Artery Disease and Aortic Stenosis with Apo(A).

A study by Moreno JA *et al.* reported that both diet and ApoE genotype affect the size of lipoprotein [34]. According to them individuals with ApoE4 carriers had bigger size of LDL. Subjects with ApoE4 carriers who were subjected to sugar-rich diet, had enlarged LDL, the exact mechanism of increased VLDL synthesis would be credited to the fatty acid oleic acid causing high triglyceride which refashioned the more slowly revolving LDL particle. In this research it was also reported that ApoE carrier had tinier LDL particle size. These smaller LDL particles do not depend on the size.

Sunny H. Zhang, *et al.* demonstrated that the knockout mice of Apolipoprotein E gene had higher level of cholesterol and subsequently after 8 months contracted coronary artery lesion as compare to wild mice [35]. The work by Sunny H. Zhang, *et al.* proved that the functional integrity of Apolipoprotein is very essential for the sequestration of lipid and subsequently protecting against dyslipidemia.

The isoforms of ApoE simply varies from one another by substituting two amino acids at two positions, however, the isoforms are rendered drastic change both in term of chemistry and physiology, which in turn would the lipid metabolism and subsequently induce cardiovascular pathology. Numerous studies in different ethnicities have shown that ApoE4 genotype is greatly related with dyslipidemia while ApoE2 is proved to be protective [36] [37] [38] [39] [40]. However, according to the study by Larifla Li *et al.* in 712 Afro-Caribbean healthy and subjects with Coronary Artery Disease did not show any relationship be-

tween Apo 4 and hyperlipidemia ($p = 0.002$) [16].

On the other hand, it has been studied in great detail that interactions between Apo-E attached to lipoprotein and LDL receptor are very significant for hyperlipidemia and CVD. For instance, Versmissen J *et al.* revealed that in patients homozygous for ApoE4, having mutated LDL receptor, had lower risk of Coronary Artery Disease (hazard ratio, 0.16; 95% CI, 0.05 - 0.58; $p = 0.005$) [41]

3. ApoE Polymorphism and Its Impact on Blood Lipid Level in Han Chinese

The China Health and Nutrition in 2012 reported a survey on the total prevalence of lipid in Chinese population was as follows: total cholesterol (TC) ≥ 6.22 mmol/L in males and females age above 18 were 4.7 and 5.11%, respectively, and the frequency rates of triglyceride (TG) ≥ 2.26 mmol/L amongst males and females were 16.7% and 9.8%, respectively [42]. Gan *et al.* showed in his prospective study amongst Han Chinese revealed that aging and menopause are the contributory factors of hyperlipidemia [42].

In addition to other acquired risk factors, there are multiple genes which have been elucidated in detail in different ethnicities including Han Chinese of China. The common genes which are responsible for hyperlipidemia and familial dyslipidemia are ApoE, LDLR, APOB and PCSK9 [43]. ApoE gene polymorphism and its relationship to lipid metabolism and the effect of anti-lipid therapy has been studied in Han Chinese. However, there are different results without confirmatory effects which can lead us for future therapy or can guide us in evidence based medicine. Since almost 90% of Chinese population comprises of Han ethnicity and approximately makes 1/5th of human race [44] therefore, any study regarding gene and polymorphism in such a huge mono-ethnic population would be more credible and less biased.

The possible associations in humans between the ApoE genotype and the blood lipid level and familial hyperlipidemia in different ethnicities of the world have been evaluated in multiple studies [45] [46]. Yongjing Xia *et al.* in 2000 conducted a study in Han Chinese from two different healthy populations of Shanghai ($n = 99$) and Beijing [47]. There was no significant difference in ApoE allele frequency in between the two populations, however, there was significant difference in their phenotype and blood serum lipid [47]. The study proved that genetic polymorphism is not solely counting for hyperlipidemia [42]. On the other the study could be biased since the population size was very small.

A similar study was conducted in 2016 in Han Chinese of Shandong by ShuYi Han *et al.* was consistent with other studies, ApoE2 carriers have lesser amount of blood total cholesterol, LDL-C and Apo-B than ApoE3 carrier and of serum TC,LDL-C, and Apo-B than ApoE3 carriers and superior levels in ApoE4 carriers in comparison to ApoE levels. There have been numerous researches piloted, however, without any clinical orientation. A proper study with prospective study needs to be done in order to approach more clinical targeted and used for the

betterment of patient.

The Response of Statin in Han Chinese with ApoE4 Allele

Published studies have proved the strong relationships between LDL-C and Coronary Artery Disease (FERENCE *et al.*, 2017; Sampson, Fazio, & Linton, 2012). Thus, Statins are one of the most broadly used cardiovascular medication, used for both treatment and prevention of cardiovascular diseases. It was emphasized by 2013 Chinese consensus that all the ACS patients should be administered with Statins irrespective to the level of lipid in the plasma and continue Statin even time-honored after the patient discharges (Schiele, Farnier, Krempf, Bruckert, & Ferrieres, 2018). However, it was displayed by Zhang W *et al.* in his prospective study in ACS patients taking Statins and followed for one year, 48% patients did not reach the target level of LDL (W. Zhang, Ji, Yu, & Wang, 2017). There has been inter-individual discrepancy in pharmacological response and as a result change the clinical outcome [48] [49]. There are numerous factors which are responsible for this inter-individual inconsistency such as patient's compliance to the medication, health status of the patient, quality of medication, stage and prognosis of the pathology and the most important but neglected factor, the genetic factor.

There are many factors involved in the non-responsiveness of statin such as drug non-compliance to medication, intolerance to Statins because of adverse effects, and individual differences in response [50]. The individual differences in response can be polymorphism of genes, related to different genes responsible for lipid metabolism.

One of the most pharmacodynamically essential genes, is the ApoE polymorphic genes, which is vital in the metabolism of lipid. Many researches have been conducted on it, however, with erratic outcomes. A meta-analysis conducted in 2009 about ApoE gene polymorphisms and impact on response to statin therapy, concluded that there is no influence of ApoE gene polymorphism on Statin pharmacology [51]. However, this meta-analysis had multiple drawbacks, such as, comparison of studies between different ethnicities, use of different types of Statins in various studies, and the most important, different age groups. Kirac D *et al.* their study disclosed that patients with ApoE4, allele who were treated with Statins were less-responders as compared to ApoE2 while ApoE2 allele had higher level of triglyceride [52]. The same trend was seen in Chinese Han patients having dyslipidemia, treated with Rosuvastatin. However the study was not statistically significant [53].

A similar type of study was conducted in Kaifeng city of China, nevertheless, in a bigger sample size, showed decreased responsiveness to Atorvastatin in patients with ApoE4. This study also showed less expression of both ApoE3/ApoE3 and ApoE3/ApoE4 but the impact on the expression of ApoE3/E3 was more obvious. This study was published in Chinese language [54]. These above mentioned studies contrast to the study, which was done in Singaporean Chinese,

reporting that ApoE3/ApoE4 have had better pharmacodynamics response to Simvastatin and Lovastatin than ApoE3/E3 [55].

The exact mechanism of ApoE isoform influence on lipid profile and response to statin therapy is related with the pattern of amino acid in ApoE isoforms. For instance, ApoE2 has less than 2% affinity in contrast to other isoforms but low lipid profile and low incidence of coronary artery disease. This is indorsed to the compensatory increment of receptor LDL-R. On the other hand, ApoE4 which attaches favorably to the triglyceride-predominant VLDL, as a result assists in speeding the clearance the VLDL particles from the plasma. This phenomenon consequences into down-regulation of the LDL-R resulting in hyperlipidemia [56]. This mechanism is further elucidated by many studies in familial hypercholesterolemia patients, who have degradation of the LDL-R. These studies have demonstrated that it is not the direct ApoE isoforms important in the response to Statin but rather the receptors of LDL-R and ApoE isoforms, which are essential in the response of statin therapy.

China is a big country, with different cuisines and slightly different life style, it would not be tranquil to stipulate the effect of one polymorphic gene on lipid profile and ApoE gene affecting the effect of Statin in just a small sample size selected. Similarly in Han population, there is different effect of ApoE on lipid profile. For instance, both the genotypes and the lipid profile were different in two different subjects of Shanghai [47]. On the other hand, numerous fragmented studies have evidenced that apolipoprotein e4 allele may have been one of the neglected potential causes for non-respond of dyslipidemia in patients treated with statin and consequently may affect the treatment plan of ischemic heart disease. Nonetheless, it is still very premature to adopt with confirmation that ApoE genotype polymorphism would affect the clinical outcome in ischemic heart disease, particularly acute coronary syndrome. Further study needs to be done in Han Chinese, with large number of sample size and with the same class of statins in order to confirm the impact of ApoE gene on the therapeutic effect of stain in coronary artery disease.

4. The Relationship of ApoE Gene Polymorphism to Acute Coronary Syndrome in Han Chinese

There are multiple case-control studies conducted concerning the ApoE genotype and Acute Coronary Syndrome in various ethnicities. Different parts of the world have displayed the relationship between ApoE genotype polymorphism and Acute Coronary Syndrome [57]-[62]. It is generally observed from these researches that ApoE2 allele is known to be protective for Coronary Artery Disease and Acute Coronary Syndrome while ApoE 4 allele is an alleged to be risk factor for Ischemic Heart Disease. However, relationship between ApoE gene polymorphism and Coronary Artery Disease has been inconsistent. For example in a study on in Afro-Caribbean subjects with CAD, there was a negative correlation between ApoE4 and Acute Coronary Artery Disease but one has to carefully ana-

lyze the conclusion since the study was with insignificant sample size, making it susceptible to more biased outcome [16].

Han Chinese which is making the largest ethnic group, counts for one fifth of world population and Han Chinese are making 90% of population of China [63]. Any study regarding ApoE genotype in such a large ethnic group would be more reliable and would be less confounding (Table 1).

As far as the frequency of ApoE genotype in Han Chinese is concerned, it is as following. E3/3 is 75%, E3/4 is 10.7% and E 2/3 while 0.60%, 1.20%, and 0.60% for E2/2, E2/4, and E4 [64]. However, the frequency of the ApoE genotype may vary from one demographic region to another, even in China in same ethnic group the frequency may vary widely. Numerous cross sectional studies and 2 meta-analysis have been conducted unto now. Both meta-analysis show positive relationship between Coronary Artery Disease and Ischemic Heart Disease [65]. Most of these studies have been conducted in Han Chinese, though with small sample size. They show inconsistent result. There are two meta-analysis recently done in Han Chinese, which shows that ApoE4 allele is one of the genetic factors associated with Coronary Artery Disease, in turn with Acute Coronary Syndrome [60] [62] [66]. These studies have only mentioned regarding Coronary Artery Disease and have not specified ACS. There is only limited number of studies in relationship to ApoE gene polymorphism and Acute Coronary Syndrome in Han Chinese [67] [68]. Bai and colleagues reported their study in Chinese while Baum *et al.* did not conducted their research in the mainland of China.

In order to get authenticity and confirmation of ApoE genotype relationship to Acute Coronary Syndrome, one has to be vigilant regarding the interpretation of the results the studies. We need further study with a bigger sample size or meta-analysis in Han Chinese. A meta-analysis was piloted in general population by Xu H and colleagues [60], which can conclude whether ApoE gene polymorphism prone or protects a subject to Acute Coronary Disease in Han Chinese. As shown in the table, the sample size of Coronary Artery Disease or Acute Coronary Syndrome (few studies) in Han Chinese. Therefore, one can see that the sample size in all of them is inadequate.

4.1. Relation between Apolipoprotein E Gene Polymorphism and Major Adverse Cardiovascular Events in Patients with Acute Coronary Syndrome

Major adverse cardiovascular events (MACE), which are the standard clinical combined endpoints to observe the long term prognosis of treatment or risk factors [69] in cardiovascular medicine. There has been merely one study till now reported regarding ApoE, which was conducted in HanChinese, of Beijing. Approximately, 200 hundred patients with myocardial infarction patients were followed for six months and demonstrated higher MACE in MI patient with ApoE gene isoform [13]. This study might have a new insight into the prognostic effect of ApoE genotype on coronary artery disease, specially, acute coronary syndrome.

Table 1. List of studies regarding the relationship of ApoE gene polymorphism and CHD in Han Chinese (Modified from “Meta-analysis of apolipoprotein E gene polymorphism and susceptibility of myocardial infarction, Xu *et al.*” [64]).

Previous studies regarding the relationship of ApoE and CAD in Han Chinese population			
Study Name	Study Year	Cases	Controls
Jie <i>et al.</i>	1989		
Zhang <i>et al.</i>	1998	96	131
Yuan <i>et al.</i>	1998	103	100
Li		95	46
Wu <i>et al.</i>	1998	114	135
Yan <i>et al.</i>	1999	93	113
Cao <i>et al.</i>	1999	78	85
Jin <i>et al.</i>	1999	50	100
Peng <i>et al.</i>	1999	220	180
Li <i>et al.</i>	2000	95	46
Wang <i>et al.</i>	2000	91	105
Zhang <i>et al.</i>	2001	91	102
Bai <i>et al.</i>	2001	50	47
Wang <i>et al.</i>	2001	54	71
Zhang <i>et al.</i>	2001	71	69
Pan <i>et al.</i>	2001	100	50
Yang <i>et al.</i>	2001	204	136
Zhang <i>et al.</i>	2001	91	102
Wu <i>et al.</i>	2002	172	286
Zhang <i>et al.</i>	2003	60	71
Gu <i>et al.</i>	2003	129	90
Yang <i>et al.</i>	2003	84	39
Liu <i>et al.</i>	2003		
Peng <i>et al.</i>	2003	150	157
Cao <i>et al.</i>	2003	37	72
Yang <i>et al.</i>	2003	40	31
Li <i>et al.</i>	2003	125	116
Sun <i>et al.</i>	2004	96	113
Yin <i>et al.</i>	2004	105	110
Liao <i>et al.</i>	2004	86	156
He <i>et al.</i>	2004	60	104
Xiao <i>et al.</i>	2005	257	224
Xiao <i>et al.</i>	2005	257	127
Feng <i>et al.</i>	2005	68	70
Zou <i>et al.</i>	2005	89	83
Pan <i>et al.</i>	2005		
Ou <i>et al.</i>	2005	200	100

Continued

Zhao <i>et al.</i>	2006	29	116
Liang <i>et al.</i>	2006	133	122
Ma <i>et al.</i>	2006	88	75
Xie <i>et al.</i>	2006	78	100
Wang <i>et al.</i>	2006	201	360
Xu. <i>et al.</i>	2007	52	60
Chu <i>et al.</i>	2007	329	220
Wang <i>et al.</i>	2007		
Ding <i>et al.</i>	2008	52	110
Ma <i>et al.</i>	2011	88	75

4.2. Mechanism of ApoE Allele in Increasing the Risk of Coronary Artery Disease

There are some proposed mechanisms, which can lead to Coronary Artery Atherosclerotic and subsequent Coronary Artery Disease but the lipid pathway is the most discussed of all is the pathways.

It is assumed that ApoE4 phenotype has extra affinity to the receptor on the hepatic cells. However, as a negative feedback, the number of receptors decrease, subsequently causing dyslipidemia and atherosclerotic plaque. The cap of the atherosclerotic plaque denudes and Acute Coronary Syndrome occurs (**Figure 6**).

On the other hand, people with ApoE2 allele are known to be protective in terms of cardiovascular diseases. In contrast to ApoE E 4, ApoE E2 has lower affinity for its receptor, which in turn causes increased number of receptors, thus leading to decreased level of plasma lipid. Thus, ApoE2 carriers are shielding to cardiovascular diseases.

Similarly, it was revealed by Cenarro A *et al.* in their case control study on autosomal dominant hypercholesteremic patients, showed that 3.1% patients, who had no mutation of LDLR, APOB, and PCSK9 mutations but mutation in ApoE gene. This mutated ApoE E protein leads to decreased numbers of receptors, which consequently primed to hypercholesterolemia [70]. From the animals studies it has been shown that those animals which were deficient in ApoE E, after three to four months of follow-up with chow-fed diet, developed atherosclerotic lesions in major systemic and pulmonary arteries [35] [71].

Alternatively, the rate of atherosclerotic lesions speeded in ApoE E knocked out mice fed with western diet. This verifies that ApoE E plays an important role in the pathogenesis of cardiovascular diseases. In addition, life style and diet have additive effect. There are no studies yet done on how much a person with particular allele of ApoE E contributes to the Coronary Artery Disease.

5. Can ApoE E Genotype Be Used as a Screening Test for Cardiovascular Diseases?

Since Apolipoprotein E phenotype has an essential contributor in the metabolism

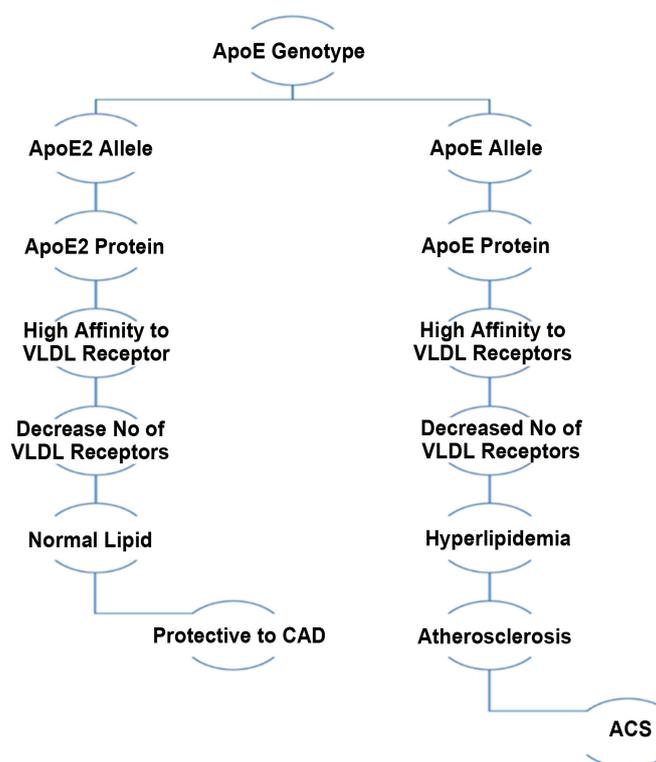


Figure 6. Illustrates the mechanism of ApoE genotype causing Coronary Artery Disease and in turn Acute Coronary Syndrome.

of any alteration in the phenotype would change both the blood lipid level and also subsequently alter the therapeutic effect of anti-lipid therapy. Now, the question is, “Can we test ApoE E gene as a screening test for healthy adults and predict the risk ratio for Coronary Artery Disease?” In addition, “Can we use test ApoE E genotype before starting anti-hyperlipidemic medication in healthy people to foreshadow the efficacy of the medication in particular those patients who are resistant to Statin?” considering the cost effect of ApoE tests. In China, ApoE test costs about 700 Chinese Yuan, which is almost equal to 120 US dollars. It would be still naïve to test individual for ApoE E genotype with such high price, which does not affect the treatment plan or one cannot yet propose any intervention with indemnity. Hence, it is prerequisite to conduct a prospective study on normal healthy adults and follow them prospectively.

6. Conclusions

In inference, although ApoE gene polymorphism might be one of the strong genetic factors contributing in the pathogenesis of hyperlipidemia, and response to Statin and most importantly in the pathogenesis of Coronary Artery Disease, especially Acute Coronary Syndrome in Han Chinese population like other populations, yet one requires to conduct a prospective study with bigger sample size in Han Chinese population.

The studies verify that ApoE4 carrier is a genetic risk factor in Han Chinese like most of the other populations while ApoE2 carrier is a genetic protective

factor. In addition, ApoE4 carrier also has higher incidence of MACE and even severe stenosis of coronary artery. However, it is still premature to agree that every patient with ACS or taking Statin for Coronary Artery Disease should be priorly tested for ApoE gene because it is not confirmed whether ApoE will assist in intervention or modify the therapeutic plan.

Despite all these reports, this zone of research still requires extensive investigations and prospective studies containing enormous size to demonstrate decisive judgment pertaining relationship of ApoE gene polymorphism with Acute Coronary Syndrome in Han Chinese population.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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