Apolipoprotein C3 gene variants and the risk of coronary heart disease: A meta-analysis

Yan Li a,⁎, Chao Li b, Jie Gao c

a Department of Epidemiology, Beijing An zhen Hospital, Capital Medical University, Beijing Institute of Heart, Lung and Blood Vessel Diseases, Beijing 100029, China
b Cardiovascular Center, Beijing Tongren Hospital, Capital Medical University, Beijing 100730, China
c Surgical Intensive Care Unit, Beijing An zhen Hospital, Capital Medical University, Beijing 100029, China

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Background: It has been reported that three common loci, SstI, C-482T, and T-455C, in the apolipoprotein C3 (APOC3) gene might be associated with an increased risk of coronary heart disease (CHD). Considering the inconsistent results and ethnicity variations, we performed a systematic meta-analysis to evaluate the association between three single nucleotide polymorphisms (SNPs) and the risk of CHD.

Methods: We searched HuGE Navigator and PubMed databases to screen for the related literature published before 25 September, 2015. Two independent reviewers extracted the data and assessed the study quality. A random-effect model was used to pool the effect size.

Results: A total of 29 studies met inclusion criteria. Nineteen studies, including 11,186 subjects relative to SstI, five studies comprising 3727 subjects relative to C-482T, and nine studies with 6753 subjects relative to T-455C were included in the final analysis. A significant increase in CHD risk was observed in the SstI polymorphism (S2 versus S1: odds ratio [OR] = 1.30, 95% confidence interval [CI] 1.10–1.55). There was also a significant increasing trend of CHD risk in the T-455C polymorphism (C versus T: OR = 1.28, 95% CI 1.16–1.41). However, no associations between C-482T and CHD risk were found in this meta-analysis.

Conclusions: The pooled evidence suggests that two SNPs (SstI and T-455C) are associated with an increased risk of CHD. However, because of the limited sample size and heterogeneity, further large-scale and well-designed studies are needed to validate our findings.

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1. Introduction

Coronary heart disease (CHD) is a complex condition caused by genetic and environmental factors (Sayols-Baxeras et al., 2014). Evidence obtained from observational studies suggests that hypertriglyceridemia is a prevalent risk factor for CHD (Abdel-Maksoud and Hokanson, 2002). However, because of the interactive effects of triglyceride (TG) with other blood lipid components, especially with an inverse association between TG and high-density lipoprotein cholesterol (HDLC), whether high levels of TG have a direct repercussion on the development of CHD, or simply represent a risk biomarker, has remained a controversial issue for a long time. TG is mostly transported in very-low-density lipoprotein (VLDL), chylomicrons (CM), and remnants of their metabolism (Nakajima et al., 2011), which are commonly referred to as triglyceride-rich lipoproteins (TRLs). Genetic association studies demonstrate that apolipoprotein C3 (APOC3) gene mutations, resulting in high circulating levels, may lead to decreased catabolism of TRLs, and have been associated with hypertriglyceridemia and CHD progression (Jorgensen et al., 2014; Tg et al., 2014).

ApoC3 is a 79-amino-acid glycoprotein and a major component of circulating TRLs that plays a key regulative role in lipoprotein metabolism (Bruns et al., 1984). Indeed, apoc3 impairs the lipolysis of TRLs by inhibiting lipoprotein lipase (Brown and Baginsky, 1972; Havel et al., 1973; Ekman and Nilsson-Ehle, 1975) and the hepatic uptake of TRLs by remnant receptors (Shelburne et al., 1980; Windler et al., 1980; Quarfordt et al., 1982). A few genetic studies suggest that the single nucleotide polymorphisms (SNPs) in the APOC3 gene may have implications for hypertriglyceridemia (Talmud and Humphries, 1997) and susceptibility to CHD (Ooi et al., 2008). Carriers of the SstI polymorphisms have higher apoC3 and TG levels (Song et al., 2015). Whether this gene variant confers an increased CHD risk is still unclear. Homozygotes for the C-482T and T-455C variants are resistant to insulin-mediated down-regulation of APOC3 gene transcription, which results in high TG levels (Li et al., 1995). However, there are inconsistent results on the relationship of these two polymorphisms and an increased risk of CHD.

Considering that most studies investigating the potential association between APOC3 gene variants and the risk of CHD have been conducted on diverse ethnic populations with limited sample size, we conducted a meta-analysis to systematically estimate the association of three polymorphisms in APOC3 gene with the risk of CHD.

2. Methods

2.1. Search strategy

A systematic search was performed in HuGE Navigator and PubMed databases. Two independent reviewers screened the literature published before 25 September, 2015, using Mesh terms “apolipoprotein C-III and coronary artery disease” or free index terms “[APOC3 or apolipoprotein C3] and [cardiovascular disease or coronary heart disease or myocardial infarction or ischemic vascular disease]”. Language was not a restrictive condition. According to the titles and abstracts of publications, duplications in the two electronic databases were identified and discussed as a decision for eliminating from the list of searched results.

2.2. Inclusion and exclusion criteria

Studies were eligible for inclusion if they met the following criteria: (1) the subject for the association of SstI, C-482T, or T-455C polymorphisms with CHD risk; (2) case–control study; (3) essential information on genotype or allele frequencies to estimate the odds ratios (ORs) and with 95% confidence intervals (CIs). Exclusion criteria included: (1) pedigree or family-based studies; (2) clinical trials; (3) animal studies; (4) editorials, comments, reviews, or short articles; (5) scarce or insufficient information on genotype or allele frequencies. Two reviewers independently assessed the original articles according to inclusion and exclusion criteria. Discrepancies were resolved via discussion in the review team.

2.3. Data extraction

Two independent reviewers extracted the original data using a standardized and consistent method. The following information were collected from each study: name of first author, year of publication, country of origin, ethnicity, available demographic characteristics of study population, genotyping methods, diagnostic criteria of CHD, numbers with each genotype or allele in cases and controls for SstI, C-482T, or T-455C polymorphisms. Any discordance was settled by discussion to reach a consensus.

2.4. Methodological quality assessment

We applied an adjusted methodological tool based on The Newcastle–Ottawa Scale (NOS) to assess the qualities of eligible studies, and the scale for methodological quality assessment was shown in a Data in Brief article (Li et al., 2016). The assessment form included seven following items: ascertainment of CHD, representativeness of cases, sources of controls, definition of controls, quality control of genotyping methods, Hardy–Weinberg equilibrium (HWE) in the control group, and sample size. Total quality scores ranged between 0 and 10 and were calculated by two independent reviewers, with a higher score representing a better quality. Disagreements were resolved by discussion.

2.5. Statistical analysis

HWE deviation for each eligible study was evaluated using the Chi-square test in control groups. To estimate the extent of the association of SstI, C-482T, or T-455C SNPs in the APOC3 gene with the susceptibility of CHD, the allelic model (SstI: S2 versus S1; C-482T: T versus C; T-455C: C versus T), heterozygote model (SstI: S1S2 versus S1S1; C-482T: CT versus CC; T-455C: TC versus TT), homozygote model (SstI: S2S2 versus S1S1; C-482T: TT versus CC; T-455C: CC versus TT), dominant model (SstI: S2S2 + S1S2 versus S1S1; C-482T: TT + CT versus CC; T-455C: CC + TC versus TT), as well as recessive model (SstI: S2S2 versus S1S2 + S1S1; C-482T: TT versus CT + CC; T-455C: CC versus TC + TT) were applied to measure pooled ORs and 95% CIs, respectively. The statistical significance level was determined by the Z-test with a two-sided P value less than 0.05.

Heterogeneity between studies was assessed by I² statistic and its statistical significance level was checked by Chi-square-based Q test. The random-effect model based DerSimonian–Laird method was applied to
pool the data from different studies irrespective of heterogeneity. Meta-regression was performed to detect the source of heterogeneity. Cumulative meta-analyses considering to the ascending date of publication or sample size were applied to identify the dynamic trends of summary estimate with evolutional time or incremental sample size. Moreover, sensitivity analysis was conducted to estimate the influence of a single study on the pooled effect size of combined studies by removing one study each time.

Potential publication bias was detected with Begg’s funnel plot and Egger’s regression test. An asymmetric funnel plot and a P value of Egger’s test less than 0.05 was considered a significant publication bias. All statistical analysis was implemented with STATA 12.0 and RevMan 5.1 software.

### 3. Results

#### 3.1. Characteristics of eligible studies

We searched HuGE Navigator and PubMed databases for 453 publications in accordance with the index strategy, of which 53 were obtained as full-text literature and screened for eligibility in the review. A total of 29 case–control studies met inclusion criteria, among which 19 studies including 11,186 subjects relative to SstI, five studies comprising 3727 subjects relative to C-482T, and nine studies with 6753 subjects relative to T-455C were included in the final analysis. Details of the study selection flow are documented in Fig. 1. There are 21 studies performing genotyping using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP), four studies with sequence-specific oligonucleotide probes (PCR-SOP), and four studies using TaqMan assay. Most of the studies were in agreement with HWE regarding genotyping distribution in control groups, except for three. Additionally, we applied a methodological scale to assess the qualities of inclusion studies, the lowest score was 5 and the highest score was 8, based on a total of a 10-point system. The characteristics and the quality scores for each study were shown in a Data in Brief article (Li et al., 2016).

#### 3.2. Meta-analysis for relationship of APOC3 gene variants with CHD risk

Pooled effect of polymorphisms from SstI, C-482T, and T-455C in the APOC3 gene on CHD risk were considered and computed under different modes of inheritance. Random-effect models were applied to compute pooled effect sizes (ORs and 95% CIs) irrespective of heterogeneity between studies. A significant increased risk of CHD with SstI polymorphism was observed in allele model S2 versus S1 (OR = 1.30, 95% CI: 1.10–1.55, P = 0.002, I² = 77%, Fig. 2); heterozygote comparison S1S2 versus S1S1 (OR = 1.21, 95% CI: 1.02–1.44, P = 0.03, I² = 65%) (Li et al., 2016); homozygote comparison S2S2 versus S1S1 (OR = 1.48, 95% CI: 1.09–2.03, P = 0.01, I² = 72%) (Li et al., 2016); dominant model S1S2/S2S2 versus S1S1 (OR = 1.27, 95% CI: 1.06–1.53, P = 0.01, I² = 72%) (Li et al., 2016); recessive model S2S2 versus S1S2/S1S1 (OR = 1.43, 95% CI: 1.09–1.87, P = 0.01, I² = 27%) (Li et al., 2016). There was also a significant increase in the trend of CHD risk from T-455C polymorphism in allele model C versus T (OR = 1.28, 95% CI: 1.16–1.41, P < 0.0001, I² = 42%, Fig. 3); heterozygote comparison TC versus TT (OR = 1.19, 95% CI: 1.07–1.33, P = 0.002, I² = 0%) (Li et al., 2016); homozygote model CC versus TT (OR = 1.77, 95% CI: 1.35–2.31, P < 0.0001, I² = 63%) (Li et al., 2016); dominant model TC/CC versus TT (OR = 1.30, 95% CI: 1.17–1.44, P = 0.00001, I² = 0%) (Li et al., 2016); recessive model CC versus TC/TT (OR = 1.57, 95% CI: 1.22–2.01, P = 0.0004, I² = 66%) (Li et al., 2016). However, no associations between C-482T and CHD risk were found in allele, heterozygote, or homozygote comparisons, with either dominant or recessive models (Fig. 4) (Li et al., 2016).
3.3. Heterogeneity

We conducted a meta-regression after adjustment for publication year, ethnicity, sex, genotyping method, and sample size to detect the source of heterogeneity. Considering that four studies on the SstI polymorphism and a single study on the C-482T polymorphism were restricted to male subjects, we categorized covariate sex into male or both sexes. In addition, all covariates information can be obtained directly from the literature except for the sample size indirectly computed by STATA software. Meta regression results in the allele model revealed that sex (P = 0.048) rather than publication year (P = 0.156), ethnicity (P = 0.502), genotyping method (P = 0.755), or sample size (P = 0.349), contributed to the source of heterogeneity. While executing the Monte Carlo validation with univariable 5000 permutations, covariates of sex (P = 0.130) became not statistically significant. Similar results have been observed using the heterozygote or homozygote comparisons, the dominant or recessive models. In contrast, no significant covariates were found to contribute to the heterogeneity of studies from T-455C or C-482T polymorphisms.

3.4. Sensitivity analysis and cumulative meta-analysis

The sensitivity analysis showed that no individual study affected summary ORs. A cumulative meta-analysis was performed by sorting by publication date or sample size, and the effect size estimate remained a stable trend.

3.5. Publication bias

No publication bias for the association between the T-455C polymorphism and CHD risk was identified by Begg's funnel plots (allelic model: T<sub>T-455C</sub> = 0.466; dominant model: T<sub>T-455C</sub> = 0.466; recessive model: T<sub>T-455C</sub> = 0.754) or Egger's regression tests (allelic model: T<sub>T-455C</sub> = 0.845; dominant model: T<sub>T-455C</sub> = 0.257; recessive model: T<sub>T-455C</sub> = 0.788). Similarly, no publication bias for the association between the SstI polymorphism and CHD risk were detected by Begg's funnel plots (allelic model: S<sub>SstI</sub> = 0.208; dominant model: P<sub>SstI</sub> = 0.050; recessive model: P<sub>SstI</sub> = 0.443) or Egger’s regression tests with allelic model (P<sub>SstI</sub> = 0.475) or dominant model (P<sub>SstI</sub> = 0.269) except for the recessive model (P<sub>SstI</sub> = 0.003). Symmetrical funnel plots were obtained in all genetic models (data not shown). However, no funnel plot or Egger’s test was performed for the association between the T-482T polymorphism and CHD risk based on the limited numbers of included studies.

4. Discussion

This meta-analysis shows that two polymorphisms, SstI and T-455C, in the APOC3 gene are associated with CHD risk. The human APOC3 gene is located in the APOA1/C3/A4/A5 gene cluster on the chromosome 11q23, and is expressed in the liver and intestine (Lai et al., 2005). Plasma apoC3 is an essential constituent of TRL particles, including CM and VLDL, and to a lesser extent of HDL (Nakajima et al., 2011). Previous research reported that apoC3 contributed to the...
The SstI polymorphism in the 3′ untranslated region (UTR) of the APOC3 gene was first described in 1983 (Rees et al., 1983). It is caused by the substitution of a cytosine to guanosine on position 3238, which results in the generation of two separate alleles, S1 and S2. The SstI site is unlikely to be functionally significant because it is located in the gene’s UTR. It was therefore proposed to act as a marker for a functional mutation elsewhere on the gene locus. There are substantial differences in frequency of the S2 allele among different ethnic groups. However, subtle discrepancies in minor allele frequencies (MAFs) of two sites, T-455C and C-482T, were observed in different ethnicities between the included studies in the present meta-analysis. The sequences between T-455C and C-482T in the promoter region of the APOC3 gene have shown a strong homology to a negative insulin-responsive element (IRE), and the presence of the mutant sequences reduced the inhibitory effect of the hormone (Li et al., 1995), but the association of these two polymorphisms with CHD susceptibility has not been established yet. So far, the SstI, T-455C, and C-482T polymorphisms are the most concerned and have been the main focus of research on APOC3 gene.

Among all 29 inclusion studies, three showed a deviation from HWE in population control. The divergence from HWE may be a sign of genotyping errors (Xu et al., 2002; Hosking et al., 2004; Salanti et al., 2005). However, the statistical power of detection minor genotyping errors by testing for HWE divergence was low (McCarthy et al., 2008), and the presence of HWE was generally not altered by the introduction of genotyping errors (Zou and Donner, 2006). Moreover, the analysis suggested that exclusion of HWE-violating studies may have resulted in loss of statistical significance of some postulated gene and disease associations. The adjustment for the magnitude of deviation from the model may also have the same consequence for other gene and disease associations (Trikalinos et al., 2006). Based on the aforementioned consideration, we did not eliminate these three studies from the meta-analysis to avoid selection bias.

Previous studies showed that variations in the APOC3 gene region might generate sex-specific effects (Kessling et al., 1992; Espino-Montoro et al., 2003; Coban et al., 2012). Meta-regression was performed after adjustment for publication year, ethnicity, sex, genotyping methods, and sample size to detect the source of heterogeneity. The results suggested that sex was one of the possible factors of heterogeneity despite the loss of statistical significance after Monte Carlo validation. In contrast, other factors were not considered as the cause of heterogeneity. Nonetheless, the existence of heterogeneity between studies is an inevitable limitation of this meta-analysis. Furthermore, case–control studies which are a common design for current available genetic reports and the relatively small numbers of eligible studies on the C-482T polymorphism influencing CHD were additional limitations of the present meta-analysis.

This study was independently completed from conception to completion, including analysis and writing. The literature search strategy differs from previous study (Zhang et al., 2016): Firstly, we performed a systematic databases search in PubMed and HuGE Navigator, which provide access to a continuously updated knowledge base in human genome epidemiology, including information on population prevalence of genetic variants and gene-disease associations. Secondly, the search terms used in the current study differs from the previous study. Thirdly, the literature search cutoff was 25 September, 2015, which includes more recent reports than previous analyses. Based on the above variations, the final references included in our study are significantly distinct. Some literatures have been included in the present study, which were not included in previous study. The current study had not overthrown previous findings, but more studies will be needed to validate the conclusions with increasing new data.

5. Conclusions

Our results suggested that carriers of the APOC3 allele mutation SstI and T-455C polymorphisms have an increased risk of CHD development. However, the association between C-482T polymorphism and CHD susceptibility has not been established, and needs to be validated in future studies.

List of abbreviations

- APOC3: apolipoprotein C3
- CHD: coronary heart disease
- SNPs: single nucleotide polymorphisms
- TG: triglyceride
- HDL-C: high-density lipoprotein cholesterol
- VLDL: very-low-density lipoprotein
- CM: chylomicrons
- TRLs: triglyceride-rich lipoproteins
- NOS: Newcastle–Ottawa Scale
- HWE: Hardy–Weinberg equilibrium
- PCR: Polymerase Chain Reaction
- PCR-RFLP: PCR-Restricion Fragment Length Polymorphism
- PCR-SOP: PCR-sequence-specific oligonucleotide probes
- ORs: odds ratios
- CIs: confidence intervals
- LPL: lipoprotein lipase
- UTR: untranslated region

Fig. 4. Forest plot of allele comparison of C-482T polymorphism (T versus C).
MAFs  minor allele frequencies
IRE  insulin-responsive element

Competing interests
The authors declare that they have no competing interests.

Authors' contributions
YL conceived of the study and participated in its design. CL and JG carried out the study searches and collected the data. YL performed statistical analyses and drafted the manuscript. All authors read and approved the final manuscript.

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