PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Association between apolipoprotein C3 Sst I, T-455C, C-482T and C1100T polymorphisms and risk of coronary heart disease
AUTHORS	Wu, Yihua; Lin, Bin; Huang, Yiwei; Zhang, Mingying; Wang, Jun

VERSION 1 - REVIEW

REVIEWER	Oliviero Olivieri Internal Medcine, Dept. of Medicine, University of Verona , Italy
REVIEW RETURNED	24-Oct-2013

GENERAL COMMENTS	Wu and colleagues evaluate the association between coronary heart disease (CHD) and the main polymorphic variants (SNPs) of the gene coding for apolipoprotein CIII (Apo C3), analyzing the available data on the topic by means of the classic approach of meta-analysis. The work addresses the need for a comprehensive review of the problem and therefore it is appropriate and useful. Overall the work seems to me linear, clearly described and well discussed. Some imprecise findings have to be however emended. 1) The biggest inaccuracy to be corrected concerns the number of individuals tested; is indeed necessary to clarify that 15591 participants are computable for Sst, but not for the other SNPs. The message should be attenuated so that it does not appear that such sample size is also valid for the other SNP. Actually, data for T455C are available for 3378 individuals, C482T for 3070 and C110T for 4662 subjects. This difference should be stressed in the abstract and in the conclusions, in general throughout the text. 2) For the results regarding T455C, it should be also stressed in discussion that most of the statistical power seems to be due to one report. 3) On the formal point of view, it should be clearly stated in Methods that among the outcomes Myocardial Infarction (MI) is also considered separately from CHD. Under this respect, the results should provide similar information for each SNP, not only for Sst. Minor changes or typing errors: - Page 4, L 39 : “correction” is probably “correlation” - Page 5 , L 39 : besides coronary artery disease, insert “MI “ - Page 10, L 39 (“to be interacted…”) and L45-46 (“They found… “: who are?) the phrases have to be rewritten - Page10, last L: see above for the comments on the sample size.

REVIEWER	Ashwani Kumar Mishra Assistant Professor of Biostatistics National Drug Dependence Treatment Centre (NDDTC) WHO Collaborating Centre for Substance Abuse All India Institute of Medical Sciences (AIIMS) Ansari Nagar
REVIEW RETURNED	28-Oct-2013

GENERAL COMMENTS	In the light of the demographic and epidemiological transition in the developing it is worthwhile to address such an important public health concern CHD. The present manuscript applies statistical approach to synthesize the research evidences and discuss them accordingly. Few vital research methodological approaches in Statistical Genomics needs to be addressed which are as follows: 1. Generally, in the scientific literature the research in CHD takes into consideration the modifiable and non modifiable risk factors. There needs to be mentioning of these in the manuscript. 2. The CHD is a major term and includes many outcomes like angina, unstable angina, myocardial infarction, arrthymia, atrial fibrillation and many other class of events. Although, the authors have described the search terms but we need to be more specific as to what constitute the CHD in the present research investigation. Might be supplementing the search term as MACE (Major Adverse Cardiac Event), may help in including more studies. 3. The major point that arise is related to the analytics of the paper. On three important points there exists no information. a) whether all the allelic frequencies of various polymorphisms in the Hardy Weinberg Equilibrium or not. Any departure from it needs to be seen and explained accordingly, b) the genotyping assay method was whether same or not across all the studies under the respective section as mentioned or not, need to have same assay method across studies, c) it is not clear as to whether the individual results of the association of various polymorphisms reported the univariate or the multivariable results. One need to see specifically in what way different studies analyzed the data. It might be the possibility that some may have done univariate, some multivariable and some matched analysis. So the uniformity in the statistical procedure for the analysis and establish the association between Sst1, T-455C and CHD. 4. There are typo at some places (page 7 adopted and results) 5. The clinical relevance of the results needs to be addressed. From the evidence based medicine perspectives it is important to address some points such as can the results be applied to patients care and whether benefits worth the harms and costs

VERSION 1 – AUTHOR RESPONSE

Reviewer #1:
1)The biggest inaccuracy to be corrected concerns the number of individuals tested; is indeed necessary to clarify that 15591 participants are computable for Sst, but not for the other SNPs. The message should be attenuated so that it does not appear that such sample size is also valid for the other SNP. Actually, data for T455C are available for 3378 individuals, C482T for 3070 and C110T for 4662 subjects. This difference should be stressed in the abstract and in the conclusions, in general throughout the text.
Response:
The reviewer's advice is beneficial. We have clarified this issue in the Abstract, Results and Discussion.

2)For the results regarding T455C, it should be also stressed in discussion that most of the statistical power seems to be due to one report.
Response:
We have stressed this issue, as shown in the Discussion section.

3) On the formal point of view, it should be clearly stated in Methods that among the outcomes Myocardial Infarction (MI) is also considered separately from CHD. Under this respect, the results should provide similar information for each SNP, not only for Sst.
Response:
At the reviewer's suggestion, the association between each polymorphism and MI risk was evaluated and demonstrated in the Abstract and Results.

Minor changes or typing errors:
- Page 4, L 39 : "correction" is probably "correlation"
- Page 5 , L 39 : besides coronary artery disease, insert "MI "
Page 10, L 39 ("to be interacted…") and L45-46 ("They found… ": who are?) the phrases have to be rewritten
- Page10, last L: see above for the comments on the sample size.
Response:
We have revised these errors accordingly.

Reviewer #2:
1. Generally, in the scientific literature the research in CHD takes into consideration the modifiable and non modifiable risk factors. There needs to be mentioning of these in the manuscript.
Response:
We have discussed this issue in the Discussion section.

2. The CHD is a major term and includes many outcomes like angina, unstable angina, myocardial infarction, arrthymia, atrial fibrillation and many other class of events. Although, the authors have described the search terms but we need to be more specific as to what constitute the CHD in the present research investigation. Might be supplementing the search term as MACE (Major Adverse Cardiac Event), may help in including more studies.
Response:
To identify potential missing articles, we further assessed the Cochrane library and supplementing the search term as MACE. More articles were evaluated though we could not include more studies for the meta-analysis, as shown in the Results section.

3. The major point that arise is related to the analytics of the paper. On three important points there exists no information. a) whether all the allelic frequencies of various polymorphisms in the Hardy Weinberg Equilibrium or not. Any departure from it needs to be seen and explained accordingly, b)

the genotyping assay method was whether same or not across all the studies under the respective section as mentioned or not, need to have same assay method across studies, c) it is not clear as to whether the individual results of the association of various polymorphisms reported the univariate or the multivariable results. One need to see specifically in what way different studies analyzed the data. It might be the possibility that some may have done , some multivariable and some matched analysis. So the uniformity in the statistical procedure for the analysis and establish the association between Sst1, T-455C and CHD.
Response:
The reviewer's advices are very important. We have mentioned the Hardy-Weinberg equilibrium and the genotyping assay method for each study in the Supplementary Table 1 and in the Results section and we evaluated and discussed the influence of them. All the included studies reported unadjusted odds ratio (OR) (or could be calculated), while only seven studies reported multivariable ORs. We have assessed and discussed this issue in the Results and Discussion sections.

4. There are typo at some places (page 7 adopted and results)
Response:
We have corrected these errors accordingly.

5. The clinical relevance of the results needs to be addressed. From the evidence based medicine perspectives it is important to address some points such as can the results be applied to patients care and whether benefits worth the harms and costs
Response:
We have discussed this in the Discussion section.