Reviewer's report

Title: Association of nineteen COX-2 gene variants to preclinical markers of atherosclerosis The Cardiovascular Risk in Young Finns Study

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Reviewer: Marcello Arca

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Authors have investigated the association of 19 SNPs located in the COX-2 gene with the presence of surrogate markers of atherosclerosis, carotid intima media thickness (CIMT) and carotid artery distensibility (Cdist), in a population cohort of 2443 young individuals (mean age 31.4 yrs) participating to the Cardiovascular Risk in Young Finns Study. Among the 19 selected SNPs, 4 were directly genotyped and 15 were estimated by imputation.

None of these SNPs were found to be significantly associated with either CIMT or Cdist.

They concluded that COX-2 gene variation was not related to early signs of atherosclerosis.

General comments

The study is interesting as it examines the controversial role of variants in COX-2 in the atherogenesis. Nevertheless the idea to consider early signs of atherosclerosis such as CIMT or Cdist as endpoints may be questionable as we can assume than inflammation may have minor role in early stages of atherogenesis, while it might may more relevant in late stages or in plaque complication. Moreover, as we known that overall genetics has a limited role in the risk of atherosclerosis, it is possible that in this cohort other factors (e.g. classical risk factors) might be more important in favoring increased CIMT thus outweighing the role of COX-2 gene.

In general, there are some limitations in the methodology, even though the manuscript is well written and the data are clearly presented: the points that must be addressed are the following:

1. It seems that the studied cohort was genotyped for other purposes (e.g. for a WGS analysis) and Authors used the data on COX-2 in a post-hoc analysis: If this true this must be more clearly stated and the main must be described. In addition must be also explained why these 19 SNPs were considered and how many of them were functionally significant.

2. It appears also that the selected SNPs have divergent effect on COX-2 activity (some with increasing and some other with lowering effect) and this may cause biases - e.g. a sort of a null effect-. This aspect must be clarified for example by clustering SNPs or creating haplotypes. Finally, it must be also estimated the amount of variability in the COX-2 gene explained by the selected SNPs.
3. To appreciate the potential role of genetic it is also important to identify the major determinant of CIMT or Cdist in the overall population. This could be done by logistic analysis considering the mayor cardiovascular risk factors. In fact, if these explain the large proportion of variation in CIMT or Cdist, it is obvious that genetics is of only minimal importance and difficult to reveal. I would suggest including in the manuscript the results of the analysis of major determinants of CIMT and Cdist in this cohort.

4. It is not clear why Authors postulated only an additive model in evaluating the effect of SNPs on the markers of atherosclerosis. It would be appropriate to test also a recessive model.

5. In the Discussion the biological significance of the SNPs must be underlined. Moreover, the potential implications of the association with cholesterol must be described.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests