Reviewer's report

Title: The association of 9p21-3 locus with coronary atherosclerosis: A Systematic Review and Meta-Analysis

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Reviewer: Inke König

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In their manuscript, the authors describe a literature search and meta-analysis on associations of the 9p21 region with severity of coronary artery disease. While this is a potentially interesting topic, there are some issues pertaining mainly to the methods employed.

Major compulsory revisions

1. Background: Please elaborate on the rationale of the study. While the association of the 9p21 region with CAD has been established, it does not become clear why this region should have an effect on CAD severity. Related to that, more details should be provided on this specific region concerning the possible functionality, relationship with other phenotypes etc.

2. Methods: The search itself needs to be described in much more detail. This includes answering the questions: which terms were searched for in which data bases at which date with which restrictions and with which connections? I was not able to reproduce even part of the search based on the descriptions. Did the authors also try to identify further studies by going through the reference lists and through personal contacts? In addition, it is not clear how many hits were made in each of the data bases before removing any duplicates, i.e., the upper part of the flow chart as recommended by PRISMA is missing.

3. Methods: The authors state that „In studies reporting > 1 SNP-outcome association, we chose the SNP not elsewhere tested in other data set ...“. Why was this done?

4. Methods: A number of different outcomes were analysed using a number of different genetic models. How was multiple testing accounted for?

5. Methods: In a related manner, how was power ensured for those outcomes with no detected association?

6. Results: Whenever results are presented for the different outcomes, please state how many studies and how many individuals were included.

7. Results: In presenting the studies, please also state which genetic variants were included for every study. Also, add further information on the genetic variants such as genotyping method, base position, allele frequencies and linkage disequilibrium.

8. Discussion: The authors are strongly encouraged to tone down the interpretation of their results considering the small effect sizes and lack of
adjustment for multiple testing, as well as lack of power estimates for the negative outcomes.

Minor essential revisions:
1. Background: Risk variants associated with CAD have increased in number, and more recent publications should be given. For example, in PMID: 23202125 46 variants are given.
2. Background: The authors speak of „the 9p21 variant“. However, 9p21 is a region that contains a number of variants.
3. Methods: Concerning the selection of studies, the authors say that „Applicable study designs included GWAS and observational studies (case-control, cohort, and cross-sectional) ...“. This is misleading, because GWAS are also observational studies (mostly case-control). Instead, a possible distinction would be GWAS and candidate association studies.
4. Methods: For the included studies, the ethnic background of the subjects is described. How was this accounted for in the analyses?
5. Methods: In the meta-analysis, three different genetic models were applied. This increases the multiple testing burden (see below) and is not really required, since information on the adequate genetic model should be provided by the original articles.
6. Results: Concerning the result on the number of diseased vessels, the authors state that „Homozygotes (HR) for the risk allele had 33.7% greater risk in the additive genetic model ...“. What does that mean in the context of a semi-quantitative measure; is it a risk increase by one vessel?
7. In table 2, please provide the p values instead of “NS”, and provide exact values instead of “<0.001”. Also, please provide the number of studies included.
8. Concerning figure 3, why is the plot shown for mortality, for which there was no effect? It would be, in my eyes, be more informative to see the heterogeneity for those outcomes with associations.
9. Discussion: The authors state that „All analysis were repeated using the add. rec. and dom. models where possible, with similar results across all 3 models“. Similar results from different genetic models do not really strengthen the results, because this is not necessarily expected.
10. Discussion: As a limitation, the authors are advised to include their selection of studies, which is restricted to association studies. Different results might be obtained if linkage and function studies were included as well, if there are any.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.
Declaration of competing interests:

I declare that I have no competing interests.