Reviewer's report

Title: Lack of association between polymorphisms of the IL18R1 and IL18RAP genes and cardiovascular risk: the MORGAM Project

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Reviewer: Medea Imboden

Reviewer's report:

The present research entitled “Lack of association between polymorphisms of the IL18R1 and IL18RAP genes and cardiovascular risk: the MORGAM Project” reports on association between 5 polymorphisms in the IL18R1 and 6 polymorphisms in the IL18RAP gene with risk of developing cardiovascular events, either coronary heart disease or stroke. In addition they report to have investigated the possibility of interaction of the SNPs mentioned above with other cardiovascular disease risk factors including variants of the IL18 gene.

Despite considerable sample size and careful study design, appropriate methods, as well as biologically plausible hypothesis neither positive association nor interaction results were found. The investigators conclude that the genetic variation in the receptor of IL-18 does not affect the risk for cardiovascular disease.

The report is very well written, however there seem to be several passages of copy-paste of their previously published reports e.g. relating to the IL18 finding in the same cohort (ref. 11). Some amendments must be made see below.

1. General comment:
This report only suffers from a minimalistic presentation of the results - probably due to the negative character of the findings.

2. Major Compulsory Revisions:

2.1 No data on the interactions tested is presented. The investigators are asked to present additional tables or figures showing their negative findings. Also the heading of this paragraph “multilocus analysis” should be termed more appropriately.

2.2 Please state how the genetic variants were selected. Both genes, IL18R1 and IL18RAP lie in close chromosomal vicinity. Did the author look at LD or common haplotypes potentially covering both genes?

2.3 A previous publication (Tiret et al.Circulation 2005; ref 9 in the manuscript) by partly the same authors contains a null finding on the association of the same genetic variants with cardiovascular disease. The author should cite this report and specify whether the present finding is an independent replication of the previous null finding. Is there overlap of the cases? If yes to what proportion?

2.4 Could the lack of association also be due to a limitation of the study? This
aspect and other potential limitations are not discussed and should be added in the discussion section.

3. Minor Essential Revisions

3.1 Genetic variants of IL18 and of its receptor have been associated with a variety of diseases involving chronic inflammatory states. The authors are invited to mention the association with asthma and atopy more prominently in the introduction and to harmonize conclusion and introduction to this respect.

3.2 The numbering of the tables needs to be appropriately changed as there are no space constraints and all data can be presented online.

3.3 Not all abbreviations were introduced in the text at their first appearance, e.g. CHD.

3.4 How was the recruitment of the majority of cases done (cases not belonging to the subcohort)? A short description would be greatly appreciated.

4. Discretionary Revisions

None

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