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

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Author's response to reviews: see over
Dear Editor,

We would like to thank you for considering our manuscript "MS: 1247520950229495 - Lack of association between polymorphisms of the IL18R1 and IL18RAP genes and cardiovascular risk: the MORGAM Project" worth of publication in your journal. As detailed below, our document, that has been read by an English native speaker, has been modified to incorporate reviewers' comments.

We hope this modified version would be suitable for publication BMC Medical Genetics Journal.

Sincerely yours
Answers to reviewers

Reviewer 1: Andrew J Sandford

Discretionary revisions

1) It is still unclear how the quality control process was performed. The authors are recommended to explain to the reader how they could detect contamination with another DNA using TaqMan SNP assays.

Quality control of the DNA was assessed just after the extraction step and not at the SNPs genotyping stage. This was not clear from the previous version of the manuscript and we are sorry for this confusion. We did our best to clarify that point as follows:

"Quality control of the extracted DNA
A central core laboratory aliquotted the DNA samples from all cohorts except the two cohorts of the prospective study PRIME. Fluorescent label PicoGreen (Invitrogen, Carlsbad, CA, USA) was used to normalize the DNA concentration prior to aliquotting. The samples were genotyped with quality control marker panel including sex-specific markers (one marker in the Y-chromosome, 2 in X-chromosome and 3 autosomal markers). Genotype-inferred gender was compared with the clinical records. The presence of discrepancies may indicate either that sample labels have been mixed or contamination with another DNA. This can be observed only when a sample of men has been mixed or swapped with a sample of women. Therefore, genotyped samples also included ~2% known duplicates, 5% blinded duplicates and negative controls. We then excluded all discrepant samples. The genotyping success rate was at least 98% for all control markers and we observed less than 0.25% genotyping errors based on the duplicate comparison. This quality control process was performed only once and independently of any planned SNP-specific genotyping."

As suspected by the reviewer, there is no straightforward method to detect contamination at the genotyping step using a taqman assay. However, contamination could be suspected in presence of discrepancies between duplicate genotypes and/or outliers in genotype clustering. In such situations, corresponding genotypes are excluded from the analysis.

2) Some language corrections would enhance the paper e.g. the new paragraph concerning the power analysis.

Our manuscript has been read by a English native reader and some corrections, in particular in the last paragraph about power analysis, were made.

Reviewer 2: Medea Imboden

Minor Essential Revisions

2.1 The term “htSNP” in the abstract and in the text is not explained and inconsistently used with “tag SNP”. Maybe the use of tag SNP is sufficiently self explaining. The authors might reconsider using “htSNP”
The term "htSNP" has been replaced by either "SNP" or tag "SNP" throughout the manuscript.

2.2 Results, section IL18R1 gene: There seems to be an error in citing the rs number of the delention variant. rs1565656 instead of rs1465656.

We thank the reviewer for pointing out this typo, and rs1565656 has been corrected into rs11465656.