Author's response to reviews

Title: Effect of the rs2259816 polymorphism in the HNF1A gene on circulating levels of C-reactive protein and coronary artery disease (The Ludwigshafen Risk and Cardiovascular Health Study)

Authors:

Marcus E Kleber (marcus.kleber@synlab.de)
Tanja B Grammer (tania.grammer@synlab.com)
Wilfried Renner (rennerw@klinikum-graz.at)
Winfried März (maerz@synlab.com)

Version: 3 Date: 27 September 2010

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

We forward you our revised manuscript titled “Effect of the rs2259816 polymorphism in the HNF1A gene on circulating levels of C-reactive protein and coronary artery disease (The Ludwigshafen Risk and Cardiovascular Health Study)”. We changed our manuscript according to the comments and suggestions made by the reviewers (changes are written in red) and hope that it is now suitable for publication in your journal.

Here is our point by point reply to the comments and suggestions of the referees:

Referee 1:

1. Perhaps the following consideration was addressed in their earlier study on CRP genotypes and CAD, but it is important here in this manuscript to establish the link between CRP and CAD in the study population. Are they even associated?

We inserted the following sentence: “In LURIC CRP is increased in CAD patients compared to healthy controls but the increase is only significant for patients with acute coronary syndromes, not for patients with stable CAD [48].”

2. Triglycerides, HDL-C and LDL-C were included in the preliminary comparisons between CAD cases and controls, and were shown to be significant covariates, yet they were not included in the association analyses. Why not?

Including LDL-C, HDL-C and TG as covariates does not change the results materially but we agree with the referee that it is better to include them. We changed the results of ANOVA and regression accordingly.

3. At the second line from the bottom of page 8 in the Discussion section, you do mean the C allele, right? You currently have it as "the G allele".

We corrected this mistake.
4. The second sentence in the background subsection of the Abstract is awkwardly constructed.

We changed the sentence to: “It is still controversial if it plays an active role in the development of cardiovascular disease.”

5. In the Results section under the subsection on association between the SNP and CRP levels, change " . . . cardiovascular risk factors like . . . " to " . . . cardiovascular risk factors, namely . . . ". The word "like" makes it sound as if the full list of risk factors were not included and you only gave several examples.

We changed this sentence like it was suggested by the referee.

Referee 2:

1. Address the power to assess effects on CAD. What effect size could confidently be expected to be observed?

We estimated the expected change in the OR for CAD according to König et al. We agree with the referee that our study has only limited power to detect such small changes in the OR for CAD. Therefore, to increase our power, we also looked for an association of rs2259816 with the Friesinger score. The Friesinger score is a quantitative index of the severity of CAD. Looking for an association of this SNP with a quantitative instead of a categorical variable increases the power and should allow us to detect even small effects.

2. Prior reports of this SNP have linked it to CAD--what are the differences with those reports?

The evidence for an association of rs2259816 with CAD was only suggestive, not conclusive. In contrast to another new locus that was reported by Erdmann et al. the locus at 12q34, for which rs2259816 was the lead SNP, did fail a more stringent threshold for an infinitely dense SNP map. Whereas the study by Erdmann et al. did present more cases and controls than our study we think that the strength of LURIC is the good characterization of all patients based on coronary angiography. We therefore have a clean and precise measurement of coronary heart disease and can apply and test different definitions (e.g. > 20% stenosis or >50% stenosis). Using a definition of >50% stenosis in at least one of 15 coronary segments did not change our results materially.

Sincerely Yours

Dr. Marcus Kleber