Reviewer’s report

Title: Inflammation gene variants and susceptibility to albuminuria in the U.S. population: analysis in the Third National Health and Nutrition Examination Survey (NHANES III), 1991-1994

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Reviewer: Alexander Teumer

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The submitted manuscript describes the associations of 60 SNPs located in 27 inflammatory response genes on the albumin-to-creatinine ratio (ACR) and albuminuria as a marker for kidney damage in three ethnical subgroups of the NHANES III study. Two types of Albuminuria were defined by dichotomizing the ACR using sex and non-sex specific cut-offs, respectively. Crude (unadjusted) and adjusted linear regression and logistic regression models, respectively, were used for association testing for each SNP and each ethnical subgroup. Furthermore, each test was carried out using two different genetic models as well as haplotype analysis.

The authors conclude to have found common polymorphisms and haplotypes in inflammation genes to be associated with albuminuria.

The paper is well written and the question posed by the authors is well defined. Nevertheless, there are major critical points in this paper.

Major Compulsory Revisions:

1. The results of the association analyses of the SNPs and the outcome are not on line with the conclusions the authors made. Looking at tables 3 to 5, SNPs were assumed to be significantly associated with the outcome if their uncorrected p-value was below 5%. Due to the number of independent SNPs, independent population subgroups, and different genetic models that were used for association testing, correction for multiple testing has to be taken into account, even if not all SNPs were most probably completely independent from each other (what the authors correctly mentioned). The authors reported FDR corrected p-values, which were not significant at a 5% level for most SNPs, nevertheless, also those SNPs were reported as significantly associated with ACR or albuminuria, respectively. Corrected p-values should be the minimal basis for reporting an association in this case. So no SNPs were significantly associated for ACR after FDR.

2. The SNP rs1800750 was the only SNP that was significantly associated with albuminuria after FDR using the crude model. It was not associated in the adjusted model anymore. The authors should discuss this behavior. Furthermore, it was noted by the authors that this SNP was not in Hardy-Weinberg-Equilibrium for the tested ethnical subgroup. This is an important issue that could have
resulted due to genotyping errors and should also be taken into account when reporting this SNP as associated.

3. For other SNPs (rs1143623, rs1800947) there was no significant association for albuminuria after FDR in the crude model but they had an extreme low p-value in the full adjusted model. Could this effect be more likely by limitations of the logistic regression model regarding the type and number of covariates used instead of being a true association?

4. The remaining significantly associated SNP after FDR, rs2070744, had an association p-value that still needs confirmation in other independent samples, especially because it was not associated in the other ethnical subgroups.

5. The authors should discuss why most of the SNPs were potentially associated only in one of the tested ethnical subgroups. Are there differences of the allele frequencies or haplotype structure of these loci among the subgroups that could explain this result? At least the allele frequencies of the SNPs and haplotype frequencies of the haplotype blocks in the ethnical subgroups used for association testing would be of interest and should be reported in a table. Does a meta-analysis or a combined analysis of the three ethnical subgroups reveal stronger associations?

6. Due to quality control issues, for all SNPs the result of a test for Hardy-Weinberg-Equilibrium should be reported.

7. Association results of an age and sex (where appropriate) only adjusted model would be informative and could help to find spurious associations due to limitations of the regression model and the type of covariates used.

8. It should be given a reference or discussed in more detail why hypertension and diabetes were not considered as covariates due to their involvement in causal pathways of chronic kidney disease, but e.g. waist-to-hip ratio and education were included as covariates.

Minor Essential Revisions:

Please describe briefly the function of the SAS/SUDAAN commands used to make the methods easier understandable for non SAS users.

The Satterthwaite-adjusted F-statistics used does not seem to be a commonly used F-statistics. Please explain the method briefly, esp. the advantages and possible limitations in this context or provide a reference.

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

**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.