Author's response to reviews

Title: N-acetyltransferase 8, a positional candidate for blood pressure and renal regulation: resequencing, association and in silico study

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Author's response to reviews: see over
To: Dr. Melissa Norton, Editor-in-Chief  
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BMC-series journals, BMC Medical Genetics

Author’s response to reviews.

Re: MS# 1499780885165491  

Tartu, Estonia  
22.12.2007

Dear BMC Medical Genetics Editors,

Dear reviewers,

Thank you for reading and valuable comments for the manuscript submitted to BMC Medical Genetics by Peeter Juhanson, Katrin Kepp, Elin Org, Gudrun Veldre, Piret Kelgo, Mai Rosenberg, Margus Viigimaa and Maris Laan “N-acetyltransferase 8, a positional candidate for blood pressure and renal regulation: resequencing, association and in silico study”.

We have modified the manuscript based on the suggestions of the two reviewers (dr. Munroe – REV#1; Dr. Pankow REV#2) and are submitting a revised version. The third reviewer (dr. Comings) did not have any concerns and advised acceptance without revision.

1. Typos and wordings have been corrected (REV #2, comment 6-9).
2. Throughout the manuscript “GFR” has been replaced by “eGFR” = estimated GRF from serum biomarker data. Classically, GFR is determined based on the creatinine clearance test using 24-hour urine samples (REV# 2).
3. The Abstract (p. 2) has been modified to reflect more precisely the content of the paper (REV #1).
4. According to suggestion of REV#1 we specified the size of the gene and the resequenced region in the Methods (p. 7).
5. According to the suggestions of REV# 2 (comment no 1 & no 5), we improved significantly the chapter in the Methods “Subjects for Association studies” including more detailed phenotype data (p. 7-9) and quality control parameters (p. 9) for serum biomarker values.
6. The Results (p. 11) have been supplemented with the detailed SNP data, comparison with dbSNP and HAPMAP. The 6 novel SNPs have been stated more clearly as “Six rare variants are novel, neither represented in dbSNP nor reported elsewhere:…” (REV #1)
7. The Result ch. “Association study for NAT8 5’upstream SNPs with blood pressure and eGFR” has been supplemented with the list of tested SNPs (REV #1; p. 12-13) and with the figure showing linkage disequilibrium patterns for the resequenced region (REV #1, comment no. 2; p. 13; Figure 3).
8. Results: The data of the association study with lipid parameters has been removed as both reviewers (REV #1, #2 comment no 4) indicated that it is out of context.

9. The Transcription Factor Binding Sites for alternative NAT8 promoter alleles was predicted additionally with Alibaba 2.1 TFBS prediction program (REV#1, p. 14).

10. The Discussion has been expanded with the references to (a) study’s limitations (REV#1; REV #2, comment no 13) (p. 16); (b) previously known promoter SNPs of candidate genes associated with hypertension (REV #1, p. 15) and (c) an example of a locus (HO-1) associated with both, renal response to nephrotoxins and the pathogenesis of hypertension (REV#2, comment 14; p. 17-18).

11. In Table 4 “ns” has been replaced by obtained p-values.

12. Addition figure (Figure 3) has been added showing the LD patterns of the resequenced region (REV #2, comment no 2)

13. In addition, the list of Acknowledgements has been extended.

Reply to the REV#2 comments 3 and 11-12.
Comment no 3: We acknowledge that the study groups included into the association tests are relatively small and we share the opinion with both reviewers that replication studies in other populations are the required to confirm the results of this pilot study. This opinion is also expressed in Discussion (p. 16). However, the scope of this report was not a full association study, but rather a fine-scale polymorphism screening and pilot association study for an unexplored positional candidate gene in BP and renal function. Association studies with two separate, non-overlapping cohorts (one for addressing association with blood pressure and the other with eGFR) suggested the potential differential role of alternative NAT8 promoter polymorphisms in the gene function.

Comment no 11: Detailed, improved description of the studied subjects is in Methods.

Comment no 12: The idea to look at the NAT8 variation among hypertensive subjects grouped based on the presence or absence of hypertensive nephropathy, is interesting for the design of future studies. However, in the current study setting the groups are too small for any reasonable statistical analysis. Also, this comparison would need careful matching of the groups based on several clinical parameters.

Yours sincerely,

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