Reviewer's report

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

Version: 1 Date: 22 November 2007

Reviewer: patricia Munroe

Reviewer's report:

General

-This paper describes a positional candidate gene for determining blood pressure; the kidney-expressed N-acetyltransferase 8 (NAT8). The authors re-sequenced the NAT8 gene and elucidated a number of new polymorphisms, they found variability to what was previously reported and greater variability than other BP-associated gene promoters. The authors suggested this was due to active gene conversion from an adjacent identical site. An exploratory association study was performed testing SNPs with blood pressure and GFR. They observed minor alleles of the SNPs in the 5’ region had a protective effect on systolic BP and kidney failure, with carriers of these displaying lower SBP and higher GFR. In silico analysis of the SNPs in the 5’ region suggests the possibility that these alleles may affect gene expression levels. This paper add important new information on NAT8, this will allow larger association studies to be performed, with correct SNP information to assess fully if it is an important gene in BP control and kidney function.

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

Abstract: I found the abstract to not clearly reflect the content of the paper. Can I suggest it is re-worded clearly stating the number of SNPs found and then describe the possible reason for the high variability and compare this data to the promoters of the potential BP candidate genes that this group has re-sequenced. I found this very interesting. The assessment of association of some SNPs with BP and GFR needs to be worded cautiously as very small numbers were tested, the authors need to include numbers here, and there has been no correction for multiple testing. Too much emphasis is given to this currently.

Results: page 9, detailed diversity……the authors need to state in the text how many SNPs they found, then location, then compare to numbers in dbSNP. What SNPs had been found in Hapmap? Table 2 nicely describes the results; this information needs to also be written in the text. Did the authors find 6 new SNPs?

Results: page 10, the authors only re-sequenced a very small region of the upstream/promoter areas from each gene. It is therefore, hard to compare the
diversity. There is currently no discussion given to what is known about the promoter/enhancer sequences of each of these other genes, we expect they will differ from each other. It is of interest that those with duplicate copies were the most variable, this needs to be expanded more in the discussion.

Results: page 10/11, association study …..The authors need to state how many SNPs they tested for association with BP and GFR, this is not clear. Also in this section, they need to be cautious in interpretation of association results. I was not really clear why SNPs in this gene were tested for association with lipid parameters.

Results: page 12; functional significance……. This was fine, although why was only one package used, predicting TFBS is not very easy, it would be good to see many packages predicting the same regions, this would confidence to the predictions.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

Methods: page 5. Re-sequencing – can the authors state size of gene, also how far up and down stream of the coding region of NAT8. Some of this is mentioned in results but also needs to be here.

Discussion: it would be good if the authors delineate functional experiments and also comment on larger association studies are required to be done to determine further the role of this gene in BP and kidney function

Discretionary Revisions (which the author can choose to ignore)

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

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

Quality of written English: Needs some language corrections before being published

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