Reviewer's report

Title: Single nucleotide polymorphisms in the apolipoprotein B and low density lipoprotein receptor genes affect response to antihypertensive treatment

Version: 1 Date: 14 July 2004

Reviewer: Martin C. C Michel

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General

Identification of factors, including SNP, which allow predicting blood pressure responses of individual hypertensive patients to a given drug is a major challenge of anti-hypertensive treatment. Therefore, the present study clearly is of interest.

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

1. The relative ease of genotyping relative to good phenotyping has led to numerous studies in which multiple more or less obvious candidate genes are being studied in a given population. This creates the problem of multiple comparison testing and hence possible reporting of false positives (as well as under-reporting of negative data). The authors apparently are aware of this problem and have addressed it by basing their statistical analysis on ANCOVA with multiple comparison correction. While this is adequate to correct for the various SNP tested within this manuscript, it does not account for the problem that the same database has apparently been used by the authors in the past to test for other SNP unrelated to lipid metabolism (e.g. references 12-14). Therefore, it would be helpful to explicitly state within the manuscript how many other SNP have already been tested based on the same database, including all those which have not been published. This information will be necessary to fully appreciate the value of the present data. In general, it may be helpful to inform readers whether the authors consider their study to be explorative or hypothesis-testing. In the former case, a statement on the number of other SNP previously tested in the same database will be sufficient. In the latter case, the number of previously tested SNP needs to be incorporated into the correction for multiple comparison testing (see also e.g. instructions for authors in a major journal in the field at www.jpharmacogenetics.com).

2. In general I am skeptical of pharmacogenetics studies involving relatively small patient numbers. In this regard I fully realize the obstacles in generating large databases of well phenotyped patients, but in general I am much more comfortable with databases of several hundred patients. As a minimum requirement I suggest that the authors carefully discuss the limitations resulting from a group size of less than 50 patients per treatment arm.

3. To allow a better judgment of the present data, it would be helpful if the authors included a table in which the allele frequencies of all tested SNP in the overall population (or the two treatment groups) are given.

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

1. In the 2nd paragraph of results the authors describe the impact of genotype at two loci on SBP and state that a similar (but not statistically significant) effect was seen for DBP. Inspection of figure
1. I did not confirm this statement to me since I found the raw data for DBP for these two SNP to be vastly different than those for SBP. Please explain or revise.
2. I found figure 1 a little difficult to read. It would become somewhat easier if SBP and DBP data for a given SNP were present within the same row, with one row for each SNP.
3. I was not sure what the purpose of figure 2 is. Either the authors consider figure 1 to be readable (I’m not fully certain on that one), then there is no need to replicate part of figure 1 as figure 2. Or the authors feel that figure 1 is not well digestable, then they should redo figure 1 in a way that makes it easier to comprehend.

Discretionary Revisions (which the author can choose to ignore)

1. The abstract would be more informative if the methods section contained information on the number of patients in the study and the drug doses being used. The results part of the abstract would benefit from some quantitative information, e.g. specification of the SNP which yielded positive results as well as the percentage of the overall blood pressure response statistically attributable to these SNP.
2. Background, 1st paragraph, last sentence: It is kind of strange to give a 16 and a 9 year old reference (#4,5) to support the claim that “currently, there are no useful … markers”. A more recent reference might be helpful, e.g. Koopmans et al. 2003, Pharmacogenetics 13: 705-713.
3. Results, 3rd paragraph: The authors describe the consequences of the two SNP on amino acid composition of the resulting protein. It would be helpful if they also add information, what this means for protein function. If nothing is known in this regard, this should specifically be stated.
4. It is the self-stated goal of the authors to find SNP which can predict blood pressure responses to a given treatment. Therefore, it would be helpful if they report not only whether blood pressure response differ significantly according to genotype but also which fraction of the total blood pressure response to a given treatment can be explained by this genotype.

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: Acceptable

Statistical review: Yes

Declaration of competing interests:

None