Reviewer’s report

Title: Polymorphisms of the insertion / deletion ACE and M235T AGT genes and essential hypertension: surprising new findings and meta-analysis of data

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Reviewer: Kristina Bengtsson Bostrom

Reviewer’s report:

General
The aim of this study by Mondry and co-workers is to investigate whether polymorphisms of the ACE and AGT genes are associated with hypertension and severity of hypertension. As the roles these polymorphisms play in hypertension are much debated it is relevant to investigate the associations in more populations--------

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

Abstract and Background: The aim of the study is to investigate how the ACE and AGT genes account for the prevalence of hypertension… But the subjects are not a random sample from the population but instead selected from blood donors that presumably are very healthy and patients from a clinic treating kidney diseases. The excess of males in the hypertensive sample also points towards selection bias. Usually hypertension is as common or even more common in women at that age (60 years). The genotypes of the AGT polymorphism were not in Hardy-Weinberg equilibrium which might also implicate selection bias.

Methods:
Is the use of antihypertensive treatment validated?
Some medications might be used for other purposes such as heart failure, angina pectoris or renal failure.

Results: There is no description of the subjects’ medical history or clinical data such as presence of obesity, diabetes, dyslipidemia and cardiovascular and kidney diseases. These conditions might influence the interpretation of the results.

Abstract and Result: There is a discrepancy between the analysis of the genotype frequencies in the AGT M235T polymorphism. The first analysis in all subjects shows that TT is more frequent in controls, but not significantly so (p=0.08) But in the OR calculation the confidence interval shows that it is significant (OR 0.52; 95%CI 0.28-0.96). How can that be?
Discussion: Could the discrepant results in the present study be due to chance? Is the impact of the AGT M235T polymorphism on hypertension so small that by chance the opposite allele could be shown to be associated with the condition? The number of TT homozygotes is very low. In the large study referred to (# 27) the over all OR is very near 1.0. The results should in any case be interpreted with care because the genotype frequencies of the polymorphism were not in Hardy-Weinberg equilibrium.

Results and Discussion of meta-analysis: The tests for heterogeneity were significant pointing at a considerable variation among the studies included. The reason for this heterogeneity should be discussed and the result of the meta-analysis should be interpreted with great caution.
Discussion: The authors should explain further why they propose a recessive effect of the T-allele on of hypertension. How could that be a conclusion from the fact that the allele frequency in the present study was below the CI of frequencies in an earlier meta-analysis (ref # 7)? Can recessive inheritance exist in a polygenic condition?

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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)

Abstract and Method: RFLP is short for restriction fragment length polymorphism.
Background: Reference # 12 (by Rigat) describes just ACE concentration in relation to the I/D polymorphism and not the association with hypertension.
Results: The I/D polymorphism does not give rise to different forms of the ACE (isoforms) so genotypes should be used instead of isoforms.
Figure 1 and 2: The number of genotype carriers should be inserted in the bars as in figure 3. In all figures the p-values (at least those < 0.05) should be inserted. The f(D)/f(T) denominations should be explained in a footnote.
Results: The order of the tables is not correct table 3 comes before table 2 in the text.
Discussion: In the reference #28 there was not shown a statistically significant decrease in the T allele frequency by age.
Figure 4 and References:
The papers included in the meta-analysis should be referred to in the figure # 4 (first author, year of publication and number in reference list). The 2 new included papers and the present study should be marked specifically. The present study seems to be presented by the author Nagel, has these results been published before?
Last sentence in Results; “no association” should be used instead of “no correlation”. The analysis is a chi-square analysis of genotype frequencies in the different subgroups according to the Methods section; no correlation analysis has been performed.
The manuscript should be scrutinized to find inconsistencies in labelling such as using “OR” in stead of “odds ratio” consequently.

Discretionary Revisions (which the author can choose to ignore)

Background: Reference # 3 seems to be a dissertation which is usually difficult for the reader to retrieve. Referring to original papers is better.
Methods: The genotyping methods are not described; in the referred works several different methods were used. A short description of the actual methods used in the present study would be useful.

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: No

Declaration of competing interests:
None