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: Christos Bantis

Reviewer's report:

General

Mondry et al investigated the influence of ACE-I/D and angiotensinogen M235T polymorphisms on essential hypertension in a cohort of 638 patients and 720 controls. This is one of the largest studies published in the field. The manuscript is well written, material and methods are sufficient. Beside the own results Mondry et al summarize all previous studies in a meta-analysis. However, there is a possibility that despite the large sample size the described associations are spurious ones. For example an impact of the M235T AGT-polymorphism on the frequency of hypertension was found only in females and not in males or in the complete cohort and could be detected only when comparing genotypes and not when comparing allele frequencies. This association is further an adverse one with no physiological background (the high angiotensinogen producing genotype being associated with decreased risk for hypertension). Giving the fact that multiple comparisons without an a-correction were made and the significance level was rather low (p<0.05) there is possibility of an error. On the other hand even unexpected data should be published, especially when they are based on large study populations, in order to avoid publication bias and ensure the correctness of future meta-analyses.

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

None.

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

Although the investigated polymorphisms are well known to the scientific community, their impact on the molecular phenotype (i.e. ACE- and angiotensinogen levels) should be mentioned in the manuscript. This way the described associations of the genotype to the clinical phenotype (hypertension) would be more comprehensive to the reader.

The term genotype should be used instead of the term isoform.

Table 2 appears in the text after table 3 and 4.

The definition of the subgroups in the combined analysis of ACE and AGT polymorphisms appears confusing to me: for example a patient with the TT/ID genotype belongs to the subgroup TT, DD/DD or to TT, II/DD or to both?
Similarly the subgroups of the reference 15 mentioned twice in the text are not well defined: “… reported that the MM (AGT-polymorphism), AA (???) , CC (???) DD/ID (ACE-polymorphism genotype combination….”

In the results section, in the paragraph “AGT polymorphism” in the first sentence the phrase “tended to be more frequent” should be used instead of “were more frequent” (p<0.08).

Similarly in the discussion section, when describing the own results concerning the impact of the investigated polymorphisms on the severity of hypertension, no positive associations should be implied since the p values are really high (p=0.185 and p=0.276).

Discretionary Revisions (which the author can choose to ignore)
The discussion section could be shortened.
Considerations about limitations in the statistical power of the study due to multiple comparisons without an a-correction should be added.

What next?: Accept after minor essential 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