Author's response to reviews

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

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Response to Dr. Bostrom’s comments:

We thank Dr. Bostrom for the in-depth comments and hope to answer convincingly this time so that she will agree with her fellow reviewer, Dr. Bantis, in accepting this manuscript for publication.

Major compulsory revisions:

“There is a large proportion (65%) of patients with kidney disease (and renal hypertension?) in the current study. This could influence the interpretation and discussion of the results of the AGT235 polymorphism in relation to other studies. The mechanisms leading to hypertension might be different in patients with kidney disease compared with the mechanisms leading to essential hypertension.”

In the methods section, we had stated that “All hypertensive patients included in the study had been diagnosed as suffering from primary hypertension by the attending consultants on first contact with the clinic.” We agree with the reviewer that the high prevalence of renal disease discovered in the course of treatment is disturbing. We have therefore added the following cautioning paragraph to the discussion section: “The study population presented here contains a large proportion (65%) of patients with renal disease. While selection of participants based on patient records excluded those patients that had symptoms suggesting the diagnosis of secondary hypertension at first contact, the possibility remains that at least a part of the study population suffers from renal rather than essential hypertension. It should be noted, however, that the majority of studies included in the presented meta-analysis does not give specific information regarding renal function of hypertensives, and the largest study (Sethi 2001) is population based and does not name any specific, kidney related exclusion criteria.”

“Further, could the AGT235 T allele and/or the TT genotype confer a higher mortality in patients with kidney disease compared with younger healthy blood donors and thus be rarer in those patients? This should be discussed.”


hypertension” gives a total of ten results. Of these, “Davis D, Liyou N, Lockwood D, Johnson A. Angiotensinogen genotype, plasma protein and mRNA concentration in isolated systolic hypertension. Clin Genet. 2002 May;61(5):363-8.” states: “Both the M235T (p = 0.0015) and G( 6)A (p = 0.029) polymorphisms were associated with ISH. Plasma angiotensinogen concentration was higher in patients than controls (p < 0.0001), but was not associated with genotype.”

As such, we find not enough evidence for an association of the 235T AGT allele with increased mortality and would prefer not to discuss this point in the manuscript.

“I don’t understand the newly added sentence (third paragraph of discussion) about the recessive inheritance pattern of the AGT235 T allele. The trait hypertension could be recessively inherited but the alleles are randomly picked from the parents.”

We have deleted this part of the sentence in the revised manuscript.

Minor essential revisions and Discretionary revisions were made according to the reviewer’s suggestions.