Reviewer’s report

Title: Association between -T786C NOS3 polymorphism and resistant hypertension: A prospective cohort study

Version: 2 Date: 27 May 2009

Reviewer: James V Gainer

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This manuscript revision pertains to a study designed to determine if polymorphisms in the endothelial nitric oxide synthase (NOS3) gene are associated with resistant hypertension.

Major Compulsory Revisions

1. In this study, a clinical definition of resistant hypertension is used which involves excluding those subjects with: a.) secondary causes of hypertension; b.) white coat hypertension; c.) inadequate dosing of antihypertensive medications; and d.) non-adherence to treatment. Detailed information regarding how subjects were included or excluded in the study, for at least each of these factors, must be delineated. Protocols and validation of measures such as analytic control and adherence tests should be included. What types of diets were subjects ingesting during the period of observation? Were dietary influences controlled during the period of blood pressure assessment? Pertaining to the assessment of target organ damage, were funduscopy and echocardiography measures validated?

- The authors note that the specific data are not available but should describe the process nevertheless, e.g. the presence of secondary hypertension determined on clinical grounds. The authors’ responses regarding funduscopy and echocardiography should be included in the manuscript.

2. A table of all baseline characteristics including statistical comparison between the resistant hypertensive and control groups should be included. This table should include several relevant factors such as body mass index or other suitable anthropometric values and lipid values. Likewise a table of antihypertensive medication use between groups would be useful. Results of the 24-hour ambulatory blood pressure assessment were not included. Details of the multivariate analysis should be included. Were multiple models investigated? The issue and handling of multiple comparisons should be explicitly specified in the methods section. It would appear that no correction of p-values for multiple
comparisons was applied in this study.

- The suggestion of including body mass index was ignored. Such a factor is needed for comparison between groups and in the multivariate analyses.
- Regarding the multiple comparisons issue, a more detailed explanation as to why this was not done should be included in the manuscript itself.

3. Acknowledgment of limitations should be explicitly included. This cohort has possibly been used other studies (J Hum Hypertens. 2009 Mar 12 - epub ahead of print) which would also have an effect on the multiple comparisons issue as noted above. This issue should be addressed.

- No response was provided as to whether this cohort was used in other studies.

Minor Essential Revisions

1. Several grammatical errors are still present. On page 4, “Once excluded the secondary causes of hypertension and those patients who did not adhere [to] lifestyle measures…”.

Discretionary Revisions

1. To provide additional perspective, the discussion would benefit from a brief synopsis of the studies of these particular polymorphisms and other nitric oxide synthase variants with respect to hypertension including references to positive, negative, and indeterminate studies.

2. Was there consideration of a haplotype analysis in any fashion?

The discussion section has been improved overall.

**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:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests.