Reviewer's report

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

**Version:** 1  **Date:** 24 March 2009

**Reviewer:** James V Gainer

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The goal of this study was to determine if polymorphisms in the endothelial nitric oxide synthase (NOS3) gene are associated with resistant hypertension. The study of genetic variation in the context of resistant or refractory hypertension is appealing because of the presumption that genetic homogeneity, and thus the potential to identify variants of larger effect, may be increased according to phenotype severity.

**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 funduscropy and echocardiography measures validated?

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.

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.

**Minor Essential Revisions**

1. Grammatical errors and awkward sentences were noted in several places. For
example, on page 2 (abstract), … “therapy could be determined at [the] endothelial level.” On page 4, “Once excluded the secondary causes of hypertension and those patients who did not adhere 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?

**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.