Reviewer's report

Title: Thrombomodulin Ala455Val Polymorphism and the Risk of Cerebral Infarction in a Biracial Population: The Stroke Prevention in Young Women Study

Version: 1 Date: 10 August 2004

Reviewer: James Meschia

Reviewer's report:

General

This is a well-written manuscript that takes advantage of a well-conceived population based study of stroke in young women. This case-control study shows that the A allele of the Ala455Val polymorphism of the THBD gene was associated with ischemic stroke in young women in the Baltimore-Washington area. The study included 141 patients and 210 controls. There was a nearly 2-fold increased risk of stroke in patients with the AA genotype relative to the AV or VV genotypes. The limitations of the study are the relatively small numbers of cases of ischemic stroke, their presumed etiological heterogeneity, and the limited genotyping of THBD (1 coding single nucleotide polymorphism (SNP)).

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):

1. Because the SNP has been associated with ischemic heart disease (references 9 and 10), it might be appropriate to include ischemic heart disease in one of the logistic regression models.
2. Readers might find it helpful to add a "part B" to the figure illustrating the molecular relationships described in the opening paragraph of the background section.
3. The population of young women has unique characteristics that are not fully presented in the paper. For example, what percent of cases/controls had the hemoglobin S mutation? What percent of women had taken oral contraceptives or hormone replacement therapy (which is of particular importance given the gene being tested)? Were there any interactions of the polymorphism with these characteristics?
4. In Table 4, the category of probable diagnosis of 'other determined cause' (which contains 38 patients) should be expanded out to better characterize the patient population.
5. The last paragraph of the results section needs to be clearer. According to the abstract, the last sentence should read, "An increased association between non-cardioembolic stroke and the AA genotype was demonstrated (odds ratio 2.2, 95% CI 1.2 to 4.2)."
6. The sentence in the results section that reads, "Stroke cases were classified as having a probable ..." should be moved to the methods section.

Discretionary Revisions (which the author can choose to ignore):

The manuscript ends after a discussion of the strengths and weaknesses of the study. While it is routine for papers to end dead-stop like this, I would argue that the authors have earned the right to
hypothesize on the potential clinical implications of their positive findings. How does the putative genetic risk factor compare in magnitude of effect to hypertension, diabetes, and other known conventional risk factors? Might testing for the SNP one day be useful in selecting secondary preventative pharmacotherapy (ie. in choosing among aspirin, warfarin, or the direct thrombin inhibitors)?

**What next?:** Accept after minor essential revisions

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No

**Declaration of competing interests:**

None.