Author's response to reviews

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

Authors:

John W Cole (jcole@som.umaryland.edu)
Stacy C Roberts (MXG2@CDC.GOV)
Margaret Gallagher (MXG2@CDC.GOV)
Wayne H Giles (hwg0@cdc.gov)
Braxton D Mitchell (bmitchel@medicine.umaryland.edu)
Karen K Steinberg (kks@cdc.gov)
Marcella A Wozniak (mwozniak@som.umaryland.edu)
Richard F Macko (rmacko@grecc.umaryland.edu)
Laurie J Reinhart (lreinhar@medicine.umaryland.edu)
Steven J Kittner (skittner@som.umaryland.edu)

Version: 2 Date: 27 October 2004

Author's response to reviews: see over
October 27, 2004

Editor-in-Chief, BMC Neurology

RE: THROMBOMODULIN ALA455VAL POLYMORPHISM AND THE RISK OF CEREBRAL INFARCTION IN A BIRACIAL POPULATION: THE STROKE PREVENTION IN YOUNG WOMEN STUDY

Dear Editor-in-Chief,

Please find attached our revised manuscript entitled “THROMBOMODULIN ALA455VAL POLYMORPHISM AND THE RISK OF CEREBRAL INFARCTION IN A BIRACIAL POPULATION: THE STROKE PREVENTION IN YOUNG WOMEN STUDY” submitted as an original research article.

The corresponding author remains John W. Cole, M.D., Department of Neurology, Bressler Bldg., Room 12-006, University of Maryland at Baltimore, 655 W. Baltimore St., Baltimore, MD 21201. (Phone 410-328-6484, Fax 410-706-0816, Email jcole@som.umaryland.edu).

We certify that we have participated sufficiently in the conceptual design of this work, the analysis of the data, and the writing of the manuscript to take public responsibility for it. We have reviewed the final version of the manuscript and approve it for publication. I participated in the writing of the initial draft, as did Drs. Kittner, Mitchell, Wozniak and Macko. Drs. Gallagher, Steinberg, Giles and Ms. Roberts participated in the genotyping. I participated in the data analysis, as did Drs. Kittner, Mitchell, and Ms. Reinhart. All authors provided critiques of the final manuscript.

If accepted for publication, the undersigned authors will transfer all copyright ownership of this manuscript to BioMed Central Ltd. The undersigned warrant that the article is original, does not infringe upon and copy right or other proprietary right of any third party, is not under consideration by another journal, and has not been published previously.

The authors have no affiliation with or involvement in an organization or entity with a direct financial interest in the subject matter or the material discussed in the manuscript. All financial project support of this research is identified in the acknowledgement in the manuscript.

Below is a point-by-point description of the changes made to the manuscript based upon the reviewer’s comments and suggestions.

Reviewer 1

1. The authors should describe in more detail, which proportion of the cases and controls from the original database are included in the present study.
   
   Two additional sentences at the end of the first paragraph in the methods section have been added to describe the case and control sample numbers in the original study as compared with the current study.

2. Matching was performed (on age and residence), but the authors fail to adjust for both matching factors, additional adjustments should be made for residence.
   
   This was the only requested change that was not performed. Unfortunately this information is not available in electronic format, hence a substantial amount of effort would be required to perform this task. However, we feel that it is unlikely
that controlling for residence would change our results. This is a genetic study involving a relatively small geographic region, and we feel that it is highly unlikely that there would be any significant genetic-based geographic clustering within any residential sub-region.

3. Terms as cohort and baseline characteristics falsely suggest a follow up study. As this is a case control study, these terms should be omitted. These terms have been omitted from the first sentence in results section.

Reviewer 2

1. Because the SNP has been associated with ischemic heart disease, it might be appropriate to include ischemic heart disease in one of the logistic regression models. Ischemic heart disease (variable name: Angina/MI) has now been included in the analyses as described in the methods section (paragraphs 3 and 4) with results documented in the second paragraph of the results section subtitled “Genotype Risk” and Tables 1-3.

2. Readers might find it helpful to add a “Part B” to the figure illustrating the relationships described in the opening paragraph of the background section. An additional figure has been included; see Figure 1. Original Figure now denoted Figure 2.

3. The population of young women has unique characteristics that are not fully presented in the paper. For example, what percentage of cases/controls had hemoglobin S mutation? What percent of women had taken OCP or HRT? Were there any interactions of the polymorphism with these characteristics? Analyses regarding these variables has been incorporated into the study as described in the Methods Section (paragraphs 3 and 4). Descriptions regarding population characteristics regarding OCP/HRT use, Sickle cell disease and trait are presented in the first paragraph of the Results section. Results of analyses regarding these variables are described in second paragraph within the results section subtitled “Genotype Risk”.

4. In Table 4, the category of probable diagnosis of other determined cause (38 patients) should be better expanded to characterize the patient population. The comment shown below is provided with Table 4 that defines in more detail the breakdown of these particular cases.

“** Other determined causes included: Probable= 38, (10 non-atherosclerotic vasculopathy, 13 hematologic, 4 migraine, 6 oral contraceptive or exogenous estrogen use, 5 other drug related). Possible=5, (3 hematologic, 2 migraine). “

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 (OR 2.2, CI 1.2 to 4.2). We would agree that the last few lines of the abstract’s results section and the last line of the manuscript’s results section were not as clearly written as they could be. We have reworded the last line in abstract’s results section to read as follows, “A secondary analysis removing all probable (n=16) and possible (n=15)
cardioembolic strokes demonstrated an increased association (odds ratio 2.2, 95% CI 1.2-4.2)."

The last line of the manuscripts results section now reads, “An increased association between non-cardioembolic stroke and the AA genotype was demonstrated (odds ratio 2.2, 95% CI 1.2-4.2). “

6. The sentence in the results section that reads, “Stroke cases were classified as having a probable ….” Should be moved to the methods section.
This sentence was moved from the Results section to the Methods section as suggested. See first paragraph Methods section.

We appreciate the critiques of the reviewers and have done our best to incorporate their suggestions into the manuscript. Thank you for considering our work.

Sincerely,
John W. Cole, M.D., M.S.
Assistant Professor of Neurology
Maryland Stroke Center
Department of Neurology
University of Maryland School of Medicine