Author's response to reviews

Title: Genome Screen in Familial Intracranial Aneurysm

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Author's response to reviews: see over
Dear Professor Graham

Thank you for the recent review of Manuscript ID 5236767492133253 – “Genome Screen in Familial Intracranial Aneurysm”. I appreciate the helpful comments from the reviewers which I believe have improved the manuscript. I describe in detail below how we have responded to each of the reviewer’s concerns. In addition, I have submitted a revised version of the manuscript in which tracking has been used to indicate all manuscript changes.

Reviewer 1

1. The discrepancies between the previous and current studies are not clearly described and the authors are encouraged to demonstrate the advantage or improved points in the current study.

Response: in response to this reviewer’s suggestion, we have added additional text to the Discussion which specifically addresses the difference in results between the earlier study and the current study and also indicates the advantage of the new study which is primarily the greater power to detect linkage resulting from the larger sample size.

2. One very important issue that has not been well approached is to detect an interaction between genetic factors and life-style represented by smoking behavior. The authors tackled this problem using ordered subset analysis (OSA). The method would be approved to examine the interaction but I have one reservation. When smokers and non-smokers have distinct genetic factors to IA, which is likely the case, this method would not be effective to extract the interaction. This possibility should be discussed.

Response: The reviewer raises an excellent point. We have performed OSA analyses to identify a potential interaction between smoking and genetic factors. However, our sample is heavily skewed towards smokers. Therefore, if the reviewer is correct that there are unique genetic factors contributing to IA in smokers and nonsmokers, we only have the power to detect genes interacting with smokers. Our limited number of low or nonsmokers is insufficient to identify genes acting in those who do not smoke. We have addressed this point in the revised manuscript by adding text to address this as a study limitation.

3. The SNP on 9q21 was detected by the genome-wide association study as being thus far the most strongly associated genetic variant with IA. Inconsistent with this evidence, the locus was not detected in the present linkage study, which suggests the insufficient sample size and power in the present study nevertheless the largest sample set so far. In general, it is well recognized that the genome-wide association
study has enhanced power to detect positive signal of common variant of modest effect comparing with the linkage study. The reason for not detecting the 9q21 locus should be mentioned.

Response: The reviewer is again correct that linkage methods do not have sufficient power to detect alleles of small effect. We have addressed this point in the revised manuscript by expanding the text in the Discussion addressing the 9q21 SNP association.

4. Table 1: Here IA is explained as intracerebral aneurysm. Consistent description is desired.

Response: We apologize for this inconsistency and have corrected Table 1.

5. Figure Non-parametric linkage results were shown in the figure. Because evidence of parametric linkage is stronger than non-parametric linkage, the result of parametric linkage might be shown.

Response: The parametric analysis was a single point analysis and was not a multipoint analysis. Therefore, it does not lend itself to a graphical presentation.

Reviewer 2

1. The authors address the advantages and most of and limitations of the study. What is not addressed well is the effect of the screening high-risk individuals. One of the criteria for high-risk is smoking. Since smoking is an important independent risk factor for IA, selecting smokers for screening may, in fact, increase the proportion of cases whose IA is predominantly due to environmental factors, i.e., whose genetic component of the disease is very low. Thus, although from a medical perspective it make sense to screen high-risk individuals, from a genetic perspective it can reduce power. Authors should address that as a potential limitation. Related questions are what fraction of cases were discovered on screening and what fraction of the families had a high proportion of screened cases?

Response: We have added a new paragraph to the Results which provides details about the study MRA. In particular, we have added text to address the number of individuals who had a study MRA, the number of families having a member with a study MRA and average and range statistics for the number of individuals obtaining a study MRA per family. We also provide now in the text the proportion of study MRAs which were positive. This information was previously only in tabular form in Table 2.

2. Linkage is a method generally not considered sensitive for detecting alleles with low relative risk or weak effect since alleles with low relative risk, or penetrance, do not result in detectable familial aggregation. Is it therefore surprising that the analysis did not detect linkage to the chromosome 9p21 risk allele? What is lowest relative risk that the study would detect?
**Response:** A similar point was raised by Reviewer 1 (item 3). As noted in the response to Reviewer 1, we have added text to the Discussion to specifically address why a linkage study would have limited power to detect a locus which has an odds ratio of 1.29.

We hope that this revised manuscript will be acceptable for publication.

If you have any questions, do not hesitate to contact me at tfroud@iupui.edu or 317-278-1291.

Sincerely,

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