Author's response to reviews

Title: A Follow-Up Study for Left Ventricular Mass on Chromosome 12p11 Identifies Potential Candidate Genes

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Author's response to reviews: see over
July 13, 2011

Dr. Jigisha Patel, MRCP, PhD
Series Editors - Medicine
BMC Medical Genetics

Dear Dr. Patel,

We are submitting our second revision of manuscript (No. MS: 1860612615208250) entitled “A Follow-Up Study for Left Ventricular Mass on Chromosome 12p11 Identifies Potential Candidate Genes” to BMC Medical Genetics.

The authors are: David Della-Morte, Ashley Beecham, Tatjana Rundek, Liyong Wang, Mark S. McClendon, Susan Slifer, Susan H. Blanton, Marco R. Di Tullio, and Ralph L. Sacco.

All changes have been marked in the manuscript. The work is original and has not been published elsewhere. It will not be submitted to another journal until a decision concerning publication has been reached by the BMC Medical Genetics journal.

Thank you for considering our manuscript for publication.
Sincerely yours,
Ralph L. Sacco, MD, MS

Answers to the critiques

We would like to thank reviewers for their insightful and constructive criticisms. We have attempted to answer each comment to the best of our abilities.

Reviewer 1

Comment 1: The abstract sentence "Twelve additional SNPs in or near 6 genes had p<0.001, indicating WC*SNP interactions in association with LVM." is misleading since having 12 SNPs with p<0.001 in 6 genes do not provide any statistical argument in favor of the presence of WC x SNP interaction if multiple testing correction for the number of (univariate and interaction) tests is correctly taken into account. I would strongly recommend the authors to temper their assertion without further replication.

Answer: We agree with the reviewer that it would be better to temper this assertion. Therefore, we changed the text of this sentence to simply state “Twelve additional SNPs in or near 6 genes had p<0.001”.

Comment 2: The rationale of the present work is justified by the results of a linkage analysis that has identified a peak signal on Chr12p11, signal that was further reinforced in a subset of families with high WC. The candidate locus, if any, should then lie in the linkage region identified in the subset of families with high WC. It is therefore not clear why a 23 - 53 Mb region is studied in the first part of the analysis and then a smaller one 23-41 in the second part. The authors should clearly explain why they did not focus their entire work on the 23-41 Mb region.

Answer: We thank the reviewer for this comment. In this study we started to look for a candidate locus associated with LVM within 23-53 Mb, the one LOD critical region of our linkage peak on Chr 12p11, prior to the OSA analysis. After
considering only the families with high WC, the evidence for linkage on Chr 12p11 increased and the one LOD critical region became smaller spanning from 23-41 Mb. Then, we focused on the narrowed peak to search for loci that might be associated with LVM only in the presence of high WC. While it is possible that the loci interacting with WC are the only loci associated with LVM under the Chr 12p11 peak, we are not assuming that to definitely be the case. There may be multiple loci associated with LVM under our linkage peak, some of which contribute to increase in LVM regardless of WC and others which contribute to an increase in LVM only in the presence of high WC. This hypothesis is supported by our data in that the SNPs that are most strongly associated with LVM in Table 2 are not the same SNPs showing the strongest interaction with WC in association with LVM in Table 3, even though many of the SNPs in Table 2 fall into the more stringent OSA critical region of 23-41 Mb. A sentence has been added in the manuscript (page 5, paragraph 3).

Comment 3: If the authors are convinced they have identified the culprit locus (or SNP), would it be possible to check whether the SNP(s) could explain the linkage signal they have observed in the previous samples.

Answer: We thank the reviewer for this suggestion. While the NOMAS sample used in this paper was a convenience sample genotyped primarily to study subclinical brain phenotypes, it was able to provide us with preliminary data. Our goal is to genotype the SNPs showing the most significant associations seen in this paper in the previous family sample to determine if they do in fact explain the linkage signal. Currently, we are pursuing funds to sequence a number of our families which will then allow us to efficiently follow up on these SNPs as well as other variations within these genes. We plan to do a thorough follow up in the family data set once we have obtained additional funding.

Other editorial requirements:

Abstract: Please ensure that the abstract in the manuscript file and on the submission system is identical.

Answer: During the resubmission we made sure that the abstract in the manuscript file and on the submission system is identical.

Tables: Please ensure that the order in which your tables are cited is the same as the order in which they are provided. Every table must be cited in the text, using Arabic numerals. Please do not use ranges when listing tables. Tables must not be subdivided, or contain tables within tables. Please note that we are unable to display vertical lines or text within tables, no display merged cells: please re-layout your table without these elements. Tables should be formatted using the Table tool in your word processor. Please ensure the table title is above the table and the legend is below the table. For more information, see the instructions for authors on the journal website.

Answer: The tables are cited in the correct order on the manuscript with Arabic numerals. The tables have been formatted as per editorial request.

Box: Unfortunately we cannot incorporate boxes. Please either change the box to a table and update any references to within the text, or include the information within the manuscript text. You can use indentation to highlight the text.

Answer: No Boxes are present in our manuscript.