Author's response to reviews

Title: A tagging SNP in INSIG2 is associated with obesity-related phenotypes among Samoans

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Author's response to reviews: see over
Title: A tagging SNP in INSIG2 is associated with obesity-related phenotypes among Samoans

Dear Editor-in-Chief,

Please find enclosed the revised manuscript referenced above. We have responded to the comments of Reviewer 3. The reviews have been very helpful for improving the quality of the manuscript. The changes in the manuscript are highlighted in ‘red’ color. We hope with the changes, the manuscript will be acceptable for publication in BMC Medical Genetics.

Thank you for your consideration.

Sincerely,
Ranjan Deka, Ph.D. on behalf of all authors

In the following, we describe how we have addressed the comments point-by-point.

Comment: We observe a decrease of D’ between third and fourth (presumed associated) hence, possibly a recombination. Do we observe this in Europeans (and in Chinese?) HapMap?
Response: Yes, the third (rs2161829) and the fourth (rs9308762) SNPs are in incomplete LD in both CEU (|D'|=0.116) and CHD (|D'|=0.285) HapMap samples.

Comment: A comparative map of the LD and haplotype between Samoans, CEU and CHN should be provided. This could help understanding where the association could lie.
Response: We have interrogated the HapMap database, which is summarized in the table below. However, in order to attain brevity in the manuscript, which is essentially a short paper, we decided not to include the table in the main body of the manuscript. Nonetheless, for perusal of the reviewer, we present the table of LD in the CEU and CHD HapMap samples here. The LD in the Samoan is already included in the manuscript (Fig 1).

<table>
<thead>
<tr>
<th></th>
<th>rs7566605</th>
<th>rs1352083</th>
<th>rs2161829</th>
<th>rs9308762</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs7566605</td>
<td>1.00 (0.110)</td>
<td>0.956 (0.443)</td>
<td>0.883 (0.449)</td>
<td></td>
</tr>
<tr>
<td>rs1352083</td>
<td>0.956 (0.443)</td>
<td>1.000 (0.222)</td>
<td>0.805 (0.067)</td>
<td></td>
</tr>
<tr>
<td>rs2161829</td>
<td>0.804 (0.207)</td>
<td>1.000 (0.491)</td>
<td>0.285 (0.070)</td>
<td></td>
</tr>
<tr>
<td>rs9308762</td>
<td>0.247 (0.006)</td>
<td>1.000 (0.120)</td>
<td>0.116 (0.003)</td>
<td></td>
</tr>
</tbody>
</table>
Comment: To sum up, is it plausible, given the LD data available both in databases and in the present study’s data that an unobserved causal variant can explain the discrepancy in results?

Let’s suppose that the functional SNP is on the 3’ side of recombinaton – explaining the absence of association with rs7566605… in Asians: then this difference is not due to an excess of LD in Samoans (Asians) but to a decrease, in this case. Maybe this should be discussed when the difference between Samoans and other ethnicities is discussed.

Response: Although, the most significant association was found with the fourth SNP in our study, we can not rule out the possibility that the functional variant is on the 5’ side. The recombination events (which is reflected by |D’| < 1) may not completely break down the correlation between rs9308762 (the 4th marker) and 5’ SNPs, which is indicated by the elevated $r^2$ (~0.4) between rs9308762 and rs7566605 (the 1st marker) in the Samoan and the HapMap Chinese samples. One possible explanation of the discrepancy is that the functional SNP is in LD with both rs7566605 and rs9308762, and is more strongly associated with rs7566605 in Caucasians and with rs9308762 in Samoans. We have added this explanation in the text, which is marked in ‘Red’ at the end of the final paragraph of the Result and Discussion section.

Comment: It is important to emphasize that the recessive model was really proposed in the initial study as the best describing the association. This should be added to the sentence which gives results of the recessive model. Obviously if the causal SNP is elsewhere, the model at the causal SNP may be different from the one at the “marker” SNP.

Response: This is a very good point. Although the recessive model was proposed in the initial study, we tested association under the additive model because of “the model at the causal SNP may be different from the one at the marker SNP”. When the marker SNP is not perfectly associated with the causal SNP ($r^2$<1), the observed level of “dominance” decreases quickly with LD – that is why we tested association under the more robust additive model. As asked by the reviewer, we have added a sentence stating that the initial study by Herbert et al. used the recessive model to fit the association signal.

Comment: Has rs9308762 been typed on any other population?

Response: Yes. This SNP has been genotyped in the 11 HapMapIII populations. The frequency of the ‘C’ allele is elevated in populations of Asian origins (i.e. CHB, CHD and JPT) compared with those of African or Caucasian descent.

Comment: It would be helpful to have a Table (similar to Table 3) where the effect sizes could be displayed. This can help spotting any possible “heterogeneity” of effects.

Response: We appreciate this important comment from the reviewer. We did not provide a detailed table for displaying the effect sizes, rather described it in the text that under additive model, each copy of C allele of rs9308762 was associated with an increase of age and gender adjusted BMI = 0.775 kg/m$^2$ and ABDCIR = 2.08 cm (Please see the highlighted sentence in ‘red’ in the first paragraph of the Results and Discussion section).