Reviewer's report

Title: Genetic variations and linkage disequilibrium block analysis on chromosome 15q14-22.1 for T2D candidate region in the Japanese population

Version: 2 Date: 31 August 2007

Reviewer: Steven Elbein

Reviewer's report:

General
This paper examines a region of replicated linkage on chromosome 15q14-22.1 (32.6-51.2 cM). The reason for choosing this region is not entirely clear, and one wonders if the real region might have been missed. Much of the data is relegated to 10 "additional files" which are not easily read. This makes the data difficult to interpret. Much data are not very helpful, whereas essential data (how much genetic variation was captured?) are not included. This is a tremendous amount of work, but in the end the results are essentially negative. The authors need to decide whether this is really the correct time to publish what is essentially a progress report.

-------------------------------------------------------------------------------------------------

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

1. The amount of genetic variation captured based on either JSNP or HapMap Asian samples should be provided. Were there gaps that were not covered? The essential information is based on r^2 rather than D'.

2. The two stage strategy would appear to lack power for effects of the size reported. Power in the Discussion is estimated on the full sample size, not on the two stage design, and even then the discussion is uninterpretable as no effect size is provided. This must be incorporated in the manuscript, based on the actual study design (2 stage), and presented with the effect sizes.

3. The introduction and Discussion are quite out of date with regard to known genes; this should be corrected.

4. The authors must show IN THE MANUSCRIPT the exact region of linkage with the 1 LOD confidence interval. Why this region was chosen is not at all clear, but is essential to the interpretation of the paper.

5. Much of the manuscript presents LD data that are available from the HapMap project. Please remove these data - this would be appropriate for supplemental files.

6. Supplemental files need to be moved into the text. Too much essential data are relegated to "additional files" that in turn are not easy to download and read. Most of these files should be included in the text. A figure showing the linkage with 1 lod confidence intervals is essential. File 3 is helpful, but the authors never
comment on the large number of SNPs tested in Stage 2 with only a single positive result. The number expected by chance in Stage 2 is 5% of the Stage 1 findings. Clearly they are below this threshold. The study is essentially negative, and likely underpowered. These issues must be addressed.

7. Correction for multiple testing is not addressed. Genotypic and allelic tests were performed. Was a correction imposed for obesity, or only age?

8. The authors should explain on Page 10 why the performed the studies of the LD block around SNP 2140 given the lack of significant association. Is there any reason to pursue URB1? Is it a candidate gene?

9. Please explain the haplotype tests. Was this an evaluation of one haplotype against all others? Did you perform an omnibus test of all haplotypes?

10. The discussion on pages 11-12 are not clear, and are not adequately explained for the reader to understand them.

--------------------------------------------------------------

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. The manuscript is redundant in several places, and needs to be shortened.

2. Given evidence for age dependency on linkage in this region, was any attempt made to examine the association by age of onset?

3. On page 15, the text in the last paragraph is difficult to understand.

4. Why publish this paper now, if in the paper the authors state that remaining genes should be tested?

5. The authors should provide some information on the UBR1 gene if they are to make the case that this is a potential diabetes gene.

6. Table 2 is not particularly useful. Tables in the additional files are more helpful. The simulation and raw p values on Table 3 are extremely similar, and see surprising for 10,000 simulations.

7. I could not successfully open File 5, but the legend suggests that this should be in the manuscript, not supplemental data. The power calculation absolutely must be in the manuscript. Figure 1 does not add that much and could be removed, but the power analysis of this strategy must be shown. Figure 2 B shows the same data twice. Overall, I wish to see the p values across the region, not the block structure. Please add that figure and take these out.

8. Figure 8 B is illegible. Overall this is not helpful. We need to see the original linkage signal. Figure 4 is totally illegible and should not be shown in this format.

--------------------------------------------------------------

Discretionary Revisions (which the author can choose to ignore)

Please make the abstract match the text. The two stage design must be explained. Insulin sensitivity is not necessarily the first defect in Caucasians; considerable data support an early role for the beta cell. This should be corrected on Page 5. Results from recent GWAS should be incorporated into the text in the introduction and discussion.
**What next?:** Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

I have no competing interests to declare.