Reviewer's report

Title: Genome Wide Association Study Identifies KCNMA1 Contributing to Human Obesity

Version: 1 Date: 2 March 2011

Reviewer: Ge Zhang

Reviewer's report:

Minor Essential Revisions

1. Page 5, line 6: “rare but highly penetrant alleles” might be better.
2. Page 6, line 1: “is about …” should be “in about …”
3. Page 6, line 2: “explained only 8kg of inter-individual variation” is not accurate. The original reference says “The difference in average BMI between individuals with a high genetic-susceptibility score (…) and those with a low genetic-susceptibility score (…) was 2.73 kg/m2, equivalent to a 6.99–8.85 kg body weight difference …”, which should not be quoted as “inter-individual variation”.
4. Page 6: Please highlight the female-biased sex ratio in Cohort 1, 2, 4 and 5. Was the bias due to the selection criteria for morbid obesity cases?
5. Page 6, line 2 from bottom: “These cohorts 1 included” might be “These cohorts included”.
6. Page 8, Genotyping Section: “500 array set” should be “500K array set”.
7. Page 9, line 11: “r2-based HapMap blocks” is not clear. Was the r2 estimated based on HapMap data? What block definition was used in building the “HapMap blocks”?
8. Page 10, Statistical analysis Section: Figure 1 should be described in this section not the Results Section.
9. Page 12, 13: The first two paragraphs overlaps substantially with the Methods Section (Cohorts, Genotyping).
10. Page 13, line 5: “21 of these SNPs” – please use a consistent number through the manuscript. This number is 22 in Table 1.
11. Table 3: The authors might consider listing the genotype counts in this table. Therefore, readers can calculate odds ratios and p-values.
12. Figure 2: Only five cohorts were included. Please check the legend (it seems that Swedish cohort 2 was missing).
13. Page 13, bottom line: The gender difference (effect of rs2116830) was not significant.
14. Table 4: Please check the numbers: $4545 = 1601 + 2943$
15. Page 14, second paragraph: “French cohort 4” should be “French cohort 5”.

16. Page 15, line 9-10: “is in close linkage …” is not an accurate description. Please clarify the LD measure (|D'| or r2). The two SNPs are not in close LD in term of r2 (0.09 based on HapMap2 CEU data).

17. Page 16, paragraph 1: Please be careful with the conclusion that “KCNMA1 seemed to have limited or no impact on BMI in the general population”. The gender, age, ethnicity and possible life style differences have not been carefully examined and controlled. Considering the potential gender difference, gender specific association test should be done in the “population samples”.

18. Page 16: The authors should discuss the biased sex ratio (comment 4) problem and discuss whether this bias can confound the association test and lead the difference between case/control test and population-based analysis.

19. Page 17, paragraph 1: The authors might consider imputation analysis to overcome this limitation (coverage of previously reported SNPs).

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

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests.