Reviewer's report

Title: Effects of smoking on the genetic risk of obesity: the Population Architecture using Genomics and Epidemiology Study

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Reviewer: Qibin Qi

Reviewer's report:

In this study, the authors examined the interactions between 10 BMI associated SNPs and smoking on BMI in a total of 13,994 African Americans and 34,233 European Americans. The overall results for SNP-smoking interaction on BMI were negative: none SNP showed significant interaction, although two SNPs showed some potential interactions with smoking status in some sub-groups stratified by race or sex. These non-significant results could be expected because of the limited statistical power for interaction analysis with individual SNPs. For FTO, the strongest BMI loci identified so far, a recent meta-analysis of ~220,000 individual only found a modest interaction between FTO and physical activity on BMI and obesity, suggesting that we may need very large sample size to detect such an interaction. The current study provides some data for gene-environment interaction on BMI, though they were negative, which might be useful for future meta-analysis. However, I have major concerns about the data presentation and interpretation. Thus, I suggested the authors to re-present the results and re-organize the paper, as their finding should be described and interpreted as negative results.

Specific comments:

1. The authors examined 10 previously identified BMI SNPs, while more than 30 SNPs have been established (in 2010). Why the author only selected 10 SNPs? For most of these cohorts participated in the current study, GWAS data should be available. Thus, it might be easy to get genotype data on other SNPs.

2. The authors stated that a p-value <0.10 were considered suggestive of interaction, which might be more clear explanation, why? Since the authors test multiple SNPs, the p-values even need adjustment for multiple tests.

3. None of the SNPs showed significant interaction with smoking on BMI. I was surprised that the conclusion is that smoking status may modify genetic effects on BMI. The authors should re-conclude their findings based on the observed negative result.

4. The authors presented some “suggestive” interaction results in some sub-group analysis as their main results. However, I think these results are not convinced. It would be better to describe all the data for each SNP rather than these 2 SNPs in sub-group analysis. Thus, table 2 could be removed. Please provide the results for 10 SNPs in European Americans for all and stratified by sex as Table 2. Similarly, please make another table for data for African
Americans. Although these data were negative, they were very informative and useful. In table 2, the columns “effect size” and “%difference in mean BMI with 1 copy risk allele” are the same meaning, right? If so, please keep one in the tables.

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

**Quality of written English:** Acceptable

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

**Declaration of competing interests:**

I declare that I have no competing interests.