Reviewer's report

Title: A polymorphism in the INSIG2 gene is not associated with obesity in a sample of 24,722 individuals from four cohorts

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Reviewer: Kiminori Yamane

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This manuscript by Bressler, et al. described the negative association between INSIG2 upstream SNP and obesity. Since many researchers have been interested in the SNP, the results would be very important to recognize the pathogenesis of obesity. However, there are critical important issues to be resolved.

Major Compulsory Revisions

1. The authors concluded that the INSIG2 SNP was not related with obesity in Abstract and Conclusions. However, the white ARIC study participants with CC genotype had lower waist-to-hip ratio compared to those with G allele. In addition, the similar result was found in African-American ARIC study subjects. Waist-to-hip ratio is known to be one of the indices for obesity. Authors should assess the discordance.

2. There were no significant differences in BMI, waist girth, or prevalence of obesity according to the genotype in each population. The authors should add comment on the power to detect association between these parameters and this SNP. Interpretation might be altered if not enough power is the reason for not finding significant difference in these parameters.

3. The first research by Herbert, et al. (Science 2006, 312:279-283) suggested that the significant relationship between the SNP and obesity was confirmed in four out of five additional cohorts, as authors also described. Authors should discuss the considerable reason why there was difference between the previous studies and present study.

Minor Essential Revisions

1. Some SNP number was stated as “rs756605”. This should be converted into “rs7566605”.

2. Some Mexican-Americans subjects in GENOA study were recruited that contained at least two siblings diagnosed as having type 2 diabetes. Diabetes might affect the body weight and body composition. Authors should consider the influence or the limitation.

3. In GENOA study, final study sample (4766 participants including 1731 African-Americans, 1421 white, and 1614 Hispanic) was likely to be larger than initially recruited sample (1228 African-Americans, 1022 Non-Hispanic white, and 954 Mexican-Americans). This was the result that it was hard to understand.
Perhaps, “additional siblings without disease (page 9, line 14)” might be included. Authors should make it clear.

4. Genotyping success rate was not perfect. How many times was the SNP determined by the system? Did authors perform direct sequence method for the determination of the SNP?


**Level of interest:** An article of limited interest

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests.