Mejía-Benítez and colleagues analyzed the effect of 6 obesity-associated SNPs located in or in proximity to FTO, NPC1, ENPP1, NEGR1, GNPDA2, and MC4R on metabolic traits and the risk of obesity in a study population consisting of lean and obese Mexican children. Of the analyzed variants, GNPDA2 rs10938397 was significantly associated with obesity, and ENPP1 rs7754561, MC4R rs17782313, and NEGR1 rs2815752 showed nominal association. In addition, MC4R rs17782313 and NCP1 rs1805081 was significantly associated with increased levels of fasting glucose and decreased levels of serum insulin levels, respectively.

This is a useful article with a clearly defined research question and a clear structure, however, several observations would require the author’s attention:

- Regarding the selection of study participants: the authors do not provide information on the grounds for excluding ~600 children who were originally recruited. Was the exclusion due to BMI selection? It should also be clarified how the 1171 non-obese children for QT studies were selected. Furthermore, are all of the study participants of ‘Mexican origin’/ethnicity?

- Regarding the selection of obesity-associated genes and SNPs: Aside from a minor allele frequency of >20% in Mexicans, the authors do not provide clear statements as to how these 6 SNPs have been selected. Have the selected genes previously been associated with obesity at a genome-wide significance level? This is relevant, as the authors later state that the association between NPC1 and ENPP1 and obesity/BMI are controversial. Furthermore, have the genes been associated with obesity in individuals of European ethnicity or also in other ethnicities? Also, several SNPs in e.g. the MC4R locus have previously been associated with obesity - have the authors selected SNPs according to lead SNPs or patterns of linkage equilibrium? The authors should include information on these issues.

- The authors identify an association between the MC4R risk allele and increased fasting plasma glucose levels, however, the authors fail to further discuss this putative association. Does this association remain significant after adjustment for BMI? Furthermore, recently published meta-analyses have in fact found variants near MC4R to associate with type 2 diabetes, both in European and Asian populations. These recent findings should be discussed by the authors. Please see the following references:


- The authors should provide a clear reference to the calculation and classification of BMI. Are the BMI percentiles based on growth curves from Mexican children?
- The authors assess the effect of SNPs using a logistic regression model adjusted for age, gender and Mexican state, however, the term Mexican state is not explained.
- It is stated that 45% of the obese children are insulin resistant. Insulin resistance should be defined.
- The power of the study and issues related to multiple testing should be discussed.
- The ENPP1 risk allele is found to be protective. Please, discuss this finding.
- In the results section, the authors provide an odds ratio confidence interval for European populations. It should be elaborated from which studies/populations these estimates have been obtained.
- OR should be included in the list of abbreviations.

Writing:
- The authors should ensure that the entire manuscript is written in past tense.
- The wording: ‘we did not find any significant contribution of both NPC1 … and FTO…’ should be corrected, e.g. to: ‘we did not find any significant contribution of either NPC1 … or FTO…’. Similar corrections should be made throughout the manuscript.
- When listing gene variants, the authors should use the same wording throughout the manuscript, e.g. MC4R rs17782313 instead of MC4R SNP rs17782313.

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