Reviewer’s report

Title: Analysis of the Relationship between MIR155HG Variants and Gastric Cancer Susceptibility

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Reviewer: Jose Saenz

Reviewer's report:

In this manuscript, Zou et al. describe a case-control study looking at the correlation between genetic variants of a miRNA, MIR155HG, and gastric cancer. In particular, they analyzed single nucleotide polymorphisms (SNPs) within this gene using a MassARRAY platform to identify particular SNPs that correlated with either increased or decreased gastric cancer risk. While I found that the overall approach of attempting to identify gastric cancer susceptibility loci is worthwhile, I believe that, in general, the authors did not adequately describe their methods and seemed to overstate certain conclusions. Some of their association analyses failed to show correlations between certain SNPs, which decreased the overall impact of the manuscript. In addition, it remains unclear whether some of their conclusions can be applied to different populations aside from the Han population in China. Perhaps the biggest weakness is that it remains to be seen how clinically and physiologically relevant the SNPs identified in this study are to gastric cancer. The authors make little to no mention of the possible functions or genetic targets of MIR155HG and how these might contribute to or prevent the progression to gastric cancer. Some additional comments are listed below:

* The introduction of the various inheritance models seems problematic to me. That the χ² test showed no statistical difference in the frequencies of any of the SNPs in the MIR155HG gene between the gastric cancer cases and controls makes it seem that the authors needed to turn to another statistical test to find an association. The authors rely on a previously published inheritance model but do not introduce the model or explain why they chose this model. What are the limitations of this model, and why would it better explain the association than the χ² test? This model appears to be central to validating the association between the SNPs and gastric cancer, so it needs to be discussed in more detail, and a more rigorous explanation of its utility needs to be made.

* The abstract presents too many loci and SNPs and no clear explanation of how these might contribute to gastric cancer. Along these lines, on p.8, lines 45-53, how are the functions of these SNPs predicted and/or validated? Are there any references to substantiate these hypothetical functions? In addition, it seems like the functions listed are fairly broad and non-specific (e.g., protein binding).

* In Table 1, what does "absence" mean for staging and LNM?

* On p.8, lines 17-23, the authors claim that "the gender distribution was statistically different between the case and control groups (p<0.05)." Is this accurate? They look nearly identical, certainly not different enough for a p value of 0.001, as shown in Table 1.

* Why are only two SNPs shown in Table 3? How did the inheritance models fare for the other SNPs shown in Table 2?

* On p. 9, lines 9-23, the authors claim that the identified SNP genotypes either increase or decrease the risk of gastric cancer. This statement, as it is worded, is not accurate. The SNP genotypes are associated with, or correlate with, an increased/decreased risk of gastric cancer, but the SNPs themselves do not increase or decrease the risk of gastric cancer. No functional validation of these SNPs was done in this study, so the authors cannot conclude that these SNPs increase or decrease the cancer risk.

* To appeal to a broader audience, the authors may want to briefly discuss the differences
between the dominant, recessive, and additive models. What does it mean for some genotypes to be correlated to gastric cancer in one model but not the other? Does this have clinical significance?

* Haplotype association analysis showed no association between specific haplotypes and risk of gastric cancer, significantly weakening the authors' conclusions.

* Are these SNPs specific to the Han population? Were other Chinese ethnicities studied or used as controls?

* No validation of the effects of these SNPs on miR-155 levels was demonstrated.

* Minor edit: On p.11, line 50, it should read "gastric cancer," not "CRC (colorectal cancer)."

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

No

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

Yes

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

No

**Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?**
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I recommend additional statistical review

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