Reviewer’s report

Title: The Int7G24A variant of transforming growth factor-beta receptor type I is a risk factor for colorectal cancer in the male Spanish population: a case-control study

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Reviewer: Yongzhan Nie

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Many studies reported that two variants in transforming growth factor-beta receptor 1 (TGFBR1), TGFBR1(*)6A and Int7G24A, A allele, have been proved to act as low-penetrance tumour susceptibility alleles in several common cancers. However, a few of studies showed negative results in breast cancer. (Br J Cancer 2007 Oct 22;97(8):1175-9. Epub 2007 Sep 11).

Castillejo et al have done a case-control study with 504 cases of sporadic CRC and same number of noncancerous controls. They provided some evidences to prove that The Int7G24A variant was associated with increased CRC incidence in an additive model of inheritance. More interestingly, the association of the Int7G24A variant with CRC risk had high significance in male patients with CRC. The data indicate that the Int7G24A variant could represent a risk factor for CRC in the male Spanish population.

I have few of major concerns which the authors need to answer.

1. Authors should well refer relevant published papers. They claimed that “there are no published reports on the association of this genetic variant with CRC”. Actually that is not true. Lindblom A group have reported relevant data on Br. J Cancer( 2007 Oct 22;97(8):1175-9. Epub 2007 Sep 11). In contrast, this study showed Int7G24A are not associated with familial CRC, hereditary non-polyposis colorectal cancer (HNPCC) and non-HNPCC. Although these two studies were performed in different populations, these controversial data would lead readers to doubt the relevance between Int7G24A and CRC.

2. In this manuscript, authors concluded that a statistically significant association of the Int7G24A variant with CRC susceptibility in the patients younger than 70 years. How did they give this threshold level? I can not imagine that the significance of association if they change the threshold into 55 or 65 years old. I would like to see the results after re-analysis based on different thresholds of age.

3. one more question about the statistics of age groups (<70 or >70). Total number of control groups is 504(284+226), however 64 patients were excluded in the experimental groups. Authors need clarify it.

4. Suggestion: some results of genotyping should be added as a figure.
Decision:
Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

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

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**
I declare that I have no competing interests