Reviewer's report

Title: The MLH1 2101C>A (Q701K) variation is related to risk of gastric cancer in Chinese males

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Reviewer: Karsten Schulmann

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The manuscript entitled „The MLH1 2101C>A (Q701K) variation is related to risk of gastric cancer in Chinese males“ by Zhi et al. Reports on data of MLH1 germline mutations in unselected 236 gastric cancer patients from two institutions in China and 240 matched controls.

They found six MLH1 sequence variants among 236 cases. No mutation was an obvious pathogenic germline mutation (frameshift, nonsense, splice site mutation, exon deletion). Five sequence variants were not associated with an increased (or decreased) gastric cancer risk compared to controls.

The 2101C>A mutation was not associated with an increased gastric cancer risk overall; however in the subgroup of males they identified an increased gastric cancer risk (OR 8.42 (95% CI 1.04-68.06) with a moderate significance level of p= 0.041. This correlation was not observed in females. In addition, they reported a correlation with younger age; however this finding was not significant.

The 2101C>A mutation was scored as tolerant using SIFT score which supports not an altered protein function.

Major points:

The section regarding the exon splicing of the 2101C>A mutation within the results is not understandable since the results and terms were not introduced in the method section. As far as the reviewer was able to conclude findings suggest an influence on the splicing effect of exon 18.

The study design is adequate. However the conclusion must be drawn very carefully. The findings regarding 2101C>A should be replicated in an independent set of gastric cancer samples (perhaps exclusively males). In addition impaired splicing should be investigated analyzing RNA transcripts. Third, the cancer of the patient should be analyzed for MSI and MMR protein expression by immunohistochemistry.

Minor points:

The authors state that the polymorphism c. -28 A>G has been so far reported exclusively in the Chinese population. However, the InSight database has a total of five entries of this mutation; one was the referenced paper from China; however there were 4 more non-Asian entries between 2001 and 2008 of this
In addition, the manuscript was written by non-native speakers and a revised manuscript needs significant editing by a native speaker.

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

**Quality of written English:** Not suitable for publication unless extensively edited

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