Reviewer’s report

Title: Identification of genetic variants for clinical management of familial colorectal tumors

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Reviewer: Judith Balmañà

Reviewer's report:

The authors present the results of their work performed in a series of 34 unrelated patients with CRC who had been previously tested for MMR and EPCAM genes and were found to be negative. A proportion of these patients had also been tested for MMR deficiency and only 2 (13%) were MSI high and the others were either negative or had not been tested. The population included patients fulfilling AMS criteria (38%) and revised Bethesda guidelines (62%). They selected a panel of 44 genes and tested them with a Truseq Amplicon-based technology. Overall, they identified one patient with a chek2 pI157T variant and 25 different VUS in their cohort, which they selected for further study by in silico analysis and minigene splicing assays. The authors conclude that the CHEK2 variant might be relevant to expand the number of genes being tested and may have clinical implications for genetic counseling and testing relatives, and they also conclude that more work is needed to better classify some of the VUS.

Despite the work is well done, it lacks some more analysis to be able to provide stronger conclusions to the readers. The CHEK2 pI157T variant has been identified in at least 5% of Northern population (mainly Finland and Poland) and in the metaanalysis it was associated with a OR 1.67 for CRC and 1.58 for breast cancer. Therefore, the actionability of this variant is still doubtful in terms of cancer screening and prevention and it requires further work.

In this regard, I'd suggest the authors to expand their cohort and simultaneously perform a case-control study to better describe the population frequency of this variant before considering it an actionable gene variant for cancer prevention.

Cosegregation analysis of VUS, as well as tumor analysis might also help in classifying the new variants.

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

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

No

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.

Not relevant to this manuscript

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