Reviewer's report

Title: MUTYH-associated colorectal carcinomas display histopathological similarities to microsatellite unstable carcinomas

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Reviewer: Milo Frattini

Reviewer's report:

The Authors investigated a cohort of MAP patients (with known biallelic germline alterations in MUTYH gene) with several markers, and then matched the results to clinico-pathological parameters. the Authors found a high frequency of CRC arising in the proximal colon, a high prevalence of tumor infiltrating lymphocytes, and a high level of K-Ras mutations (investigated by direct sequencing. for the first two features abovementioned, the Authors concluded that MUTYH CRCs show similarities to CRCs characterized by microsatellite instability.

a careful revision of the paper and of the data must be performed before any definitive evaluation

major compulsory comments

- CRCs from MUTYH arise following the Vogelgram, with MUTYH alterations that leads to APC mutations. the authors found a relative low frequency of APC mutations, they investigated only the MCR where at least 60% of APC mutations occur: the authors must revise the tissue used for DNA extraction, and must describe the percentage of tumoral cells in these blocks. alternatively, the authors should investigate the entire exon 15.

- the Authors found an abnormal high frequency of K-Ras mutations (on average 40-50%), almost exclusively characterized by the change c.34G>T. as this type of alterations, although frequent, occur in about 30-40% of K-Ras mutated cases, a contamination of K-Ras muteated allele is possible. the Authors must repeat the DNA extraction in a clean area, without any contamination, and repeat the experiments at least twice.

- the high frequency of K-Ras mutation, if confirmed, is not shared with CRC characterized by microsatellite instability. the Authors must underline this difference

- As the carcinogenesis followed by MUTYH patients is dramatically different with respect to that followed by CRC with microsatellite instability, the Authors must explain, or at least hypothesize, the observed histopathological similarity.

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

Quality of written English: Acceptable
Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

'I declare that I have no competing interests’