Reviewer's report

Title: Early onset MSI-H colon cancer with MLH1 promoter methylation, is there a genetic predisposition

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Reviewer: Johannes Gebert

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The manuscript by van Roon et al. deals with the potential causes of MLH1 promoter methylation in early onset (<50 y) sporadic MSI-H colon cancers. CIMP marker methylation levels, occurrence of somatic mutations in candidate genes (BRAF, KRAS, GADD45A, MLH1 polymorphism) as well as chromosomal alterations were determined. In addition, germline MLH1 methylation and germline GADD45A mutations were sought.

Although the authors addressed an interesting question and used several different approaches they did not uncover the cause for MLH1 methylation in this patient subset. Most of the findings represent phenomenological observations and are based on a small number of cases. Several observations in this study just confirm previous work. Overall, these results do not provide novel insights into the etiology of MLH1 promoter methylation in sporadic early onset MSI-H CRC.

In particular, the authors identified a germline MLH1 epimutation associated with female gender, proximal location and a Lynch Syndrome family history. Such cases are well known from the literature. Also, the occurrence of copy number abnormalities in MSI-H sporadic colorectal has been previously reported. Moreover, the increased CIMP-high frequency with increasing age and concomitant BRAF mutations is well established.

As one of the major conclusions the authors claim that there appears to be a subset of early onset tumors that show locus-specific methylation (MLH1 restricted) and lack of BRAF mutations. Again, a larger sample size would be required to validate this conclusion. Since choice of markers can affect the determination of CIMP, it would be important to confirm the proposed subset with a novel and extended panel of validated and CIMP-high specific methylation markers (e.g. Nosho et al. 2008; Ahlquist et al. 2008).

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

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