Reviewer's report

Title: Exome sequencing characterizes the somatic mutation spectrum of early serrated lesions in a patient with serrated polyposis syndrome (SPS)

Version: 0 Date: 18 Oct 2017

Reviewer: Daniel Buchanan

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Horpaopan et al describe the characterization of 11 serrated polyps for somatic mutations from one individual with diagnosis of serrated polyposis syndrome. The serrated polyps were distributed from the caecum to the descending colon and included sessile serrated and hyperplastic polyp subtypes. 5 demonstrated BRAF V600E somatic mutation and 1 was positive for KRAS p.G12D somatic mutation while 5 were wildtype for both. Seven somatic missense variants (validated by Sanger) in genes not previously associated with serrated pathway tumorigenesis were identified but only 2 were predicted to be likely pathogenic, ABI3BP p.K679M and CATSPERB p.P770H. The significance of these two variants and their role in the early serrated neoplasia is unknown as they were both identified in the same polyp. The results, as presented, suggest that at the least the hyperplastic polyps in the descending colon with no BRAF or KRAS mutation do not have any other somatic mutations as part of early tumorigenesis, thus are the authors suggesting that the early changes are all epigenetic? Could there have been over-filtering of variants? The somatic mutation identified in the 7 SSA/Ps with BRAF in the Sakai et al study, mentioned in the discussion of this paper, were these variants (and other key serrated pathway genes like RNF43) checked for regions of low coverage or poor sequence mapping as potential reasons for not observing them in the current study?

Otherwise well written manuscript that adds to our understanding of serrated polyposis and serrated pathway tumorigenesis.

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