Author’s response to reviews

Title: Prevalence and Spectrum of MLH1, MSH2, and MSH6 Pathogenic Germline Variants in Pakistani Colorectal Cancer Patients

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Version: 3 Date: 13 Sep 2019

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Point-by-point response to the comments of the reviewers HCCP-D-18-00030R2

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Reviewer #1 Minor revision

General comments

Point 1: Briefly describe the definition of recurrent variants which were found in the study
As per reviewer’s recommendation, we have briefly described the definition of recurrent variants (please see Methods section, page 7, 3rd paragraph, lines 21-22).

Point 2: Page 13, line 19: Patients and tumor characteristics by variants status.

"The index CRC patients with pathogenic/likely pathogenic MLH1/MSH2 variants (n=11)" is contradictory as previously described (in the text). "Seven distinct pathogenic/likely pathogenic MLH1/MSH2 variants were identified in 10 cases (10/29; 34.5%)" Have you identified 10 or 11 cases with pathogenic/likely pathogenic variants?

Please note that overall we have identified eight distinct pathogenic/likely pathogenic variants in 12 cases: 10/29; 34.5% in group 1 (HNPPCC/suspected-HNPPCC patients) and 2/183; 1.1% in group 2 (non-HNPPCC patients).
Of these 12 cases, one index patient had a diagnosis of breast and endometrial cancer and the remaining 11 were index CRC patients. In the statement "The index CRC patients with pathogenic/likely pathogenic MLH1/MSH2 variants (n=11)" (result section, Patient and tumor characteristics by variant status, page 13, line 9), tumor characteristics of these 11 CRC cases with pathogenic/likely pathogenic variant are compared with 199 CRC cases without any pathogenic/likely pathogenic variant.

Whereas, earlier in the result section "Seven distinct pathogenic/likely pathogenic MLH1/MSH2 variants were identified in 10 cases (10/29; 34.5%)" (see Results section, Pathogenic germline variants: HNPCC/suspected-HNPCC group, page 9, line 24-25), please note here we are describing those pathogenic/likely pathogenic variants identified in HNPCC/suspected-HNPCC patients ONLY (group 1).

Please note that pathogenic germline variants in non-HNPCC group are described separately in the following section (see Results section, Pathogenic germline variants: non-HNPCC group, page 11, line 21).

Point 3: Discussion: Page 14, line 2: Correct the right number of different pathogenic/likely pathogenic variants found in the study. In the discussion part: "eight different pathogenic/likely pathogenic variants found in the study". In the abstract and results part: seven.

In the abstract section: Please note that overall we have identified eight distinct pathogenic/likely pathogenic variants in our study (including group 1 and group 2) and it is now further clarified in the abstract section (please see Abstract section, page 3, lines 12 and 14).

In the results section: Please note that we are separately describing pathogenic germline variants in HNPCC/suspected-HNPCC group (7 distinct pathogenic/likely pathogenic variants) and non-HNPCC group (1 pathogenic variant that is also identified in HNPCC/suspected-HNPCC and 1 distinct pathogenic variant identified only in non-HNPCC group). But the total number of pathogenic/likely pathogenic variants would remain the same i.e. 8.

Hence, the number of different pathogenic/likely pathogenic variants found in the study is correct (please also see our response to point 2).

Point 4: Check/correct the numbers of pathogenic/likely pathogenic variants and the index CRC harboring along the manuscript.

The numbers of pathogenic/likely pathogenic variants and the number of patients harboring these variants are checked and a further clarified in abstract part (please see our response to point 2 and 3).