Author's response to reviews

Title: Breakpoint characterization of a novel large intragenic deletion of MUTYH detected in a MAP patient: Case report

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Prof Maurizio Genuardi
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Ref: MS: 1029321632571047

Dear Dr. Maurizio Genuardi

Thank you very much for the assessment of our manuscript “Breakpoint characterization of a novel large intragenic deletion of MUTYH detected in a MAP patient: Case report” (MS: 1029321632571047).

We have submitted a revised version of the manuscript, which has been uploaded with 'tracked changes' of all the corrections, where we clarify the following requested points:

1. Abstract: it should be explicitly stated that this is the second case with a MUTYH large deletion, and that the rearrangement is likely (or apparently) the same as the previously reported one.

   The following sentence was added to the “Case presentation” section of the abstract: This is the second description of this rearrangement, which has been recently described as the first large deletion in this gene.

2. p.3, Introduction, last paragraph. Delete the sentence "This deletion ... rearrangement", since it is not clear if this refers to the previous or to the current report. In addition, the sentence immediately following, beginning with "We have identified .." should be rephrased, i.e. "We have refined the breakpoint of this >4.2 kb deletion to the base pair level".

   This sentence was corrected as requested.

3. p. 4, 2nd paragraph. It is not clear whether the second group of patients - APC/MUTYH-positive - have mutations in APC or, some of them, also in MUTYH; if the latter is true, are MUTYH mutations only monoallelic or also biallelic? Furthermore, if the group contains MUTYH mutation carriers, it would be better to specify how many are APC-pos, MUTYH monoallelic, and, if applicable, MUTYH biallelic.
This paragraph was rephrased as following: In addition, the presence of this \textit{MUTYH} deletion was screened through PCR in other 183 Brazilian individuals: three \textit{APC/MUTYH}-mutation negative and 18 \textit{APC/MUTYH}-mutation positive polyposis patients (12 \textit{APC} mutation carriers, 5 \textit{MUTYH} biallelic and one \textit{MUTYH} monoallelic mutation carriers); 51 clinically suspected Lynch syndrome patients (fulfilling Amsterdam II or Bethesda criteria), who were non-carriers of germline mutations in the mismatch repair (MMR) genes \textit{MLH1}, \textit{MSH2}, \textit{MSH6} and \textit{PMS2}; and 111 healthy controls.

4. p. 5, 2nd paragraph. Rephrase the last sentence, not quite clear in the current version. Perhaps explicit mention of uniparental disomy and of heterozygosity in a single parent would be helpful. Homozygosis should corrected into "homozygosity".

This paragraph was rephrased as following: Another potential explanation for the homozygosity is the occurrence of isodisomy, a type of uniparental disomy that results in two identical segments from one parental homologue and can occur due to a recombination event in the zygote, though the existence of an affected sibling does not support this hypothesis.

On behalf of my colleagues, I want to thank you for your suggestions and hopefully the current version of our manuscript will meet your expectations.

We appreciate your attention and time.

Sincerely yours,

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