Reviewer’s report

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

Version: 2 Date: 13 August 2011

Reviewer: Astrid Out

Reviewer’s report:

The authors describe the first large CNV in the MUTYH gene, in which until recently only simple nucleotide variants had been reported. The described Brazilian polyposis patient carries a homozygous 4 kb deletion from intron 3 until after the last exon 16, which likely results in absence of MUTYH protein expression. These findings have important implications for mutation screening in familial polyposis patients, in the MUTYH gene in particular. The paper is well written and shows thoughtful reasoning. The reviewer recommends it for publication, and gives only minor text comments and some speculative remarks to add if appropriate.

Discretionary Revisions:

1. In order to find more patients with the large MUTYH deletion, the authors have screened a relatively small group of MMR gene mutation negative Lynch syndrome patients and controls, without detecting the MUTYH deletion. Overall, MUTYH mutations are rare in Lynch syndrome patients, supporting the fact that the deletion was not found in the group of 50 patients (see e.g. Riegert-Johnson et al. 2007, Stormorken et al. 2006). It would be more interesting to screen a large group of (APC-mutation negative) polyposis patients. The reviewer suggests discussing this in the paper. How many polyposis patients were screened before this deletion was found in patient FAP15?

2a. The authors explain a plausible mechanism by which the mutation might have occurred. However, the question remains when it has occurred. It might be a new variant, but it seems not unlikely that the homozygous variant in this patient (without consanguineous parents), results from inheriting two alleles of a founder mutation in the population. Another possibility could be a recombination event in the zygote, resulting in the biallelic state. Unfortunately no DNA analysis was possible for the parents and the affected sibling. It might be interesting to discuss these possibilities in the paper.

2b. It has been shown that the MUTYH gene variation spectrum differs among ethnicities. Until now most described MUTYH associated polyposis patients are of European descent, in which this deletion has not yet been found. The described variant might be a founder variant in the Brazilian population, perhaps in a subpopulation of non-European descent. This might mean that this variant also causes polyposis in descendants of the same population in other areas of
the world. The primers used for MUTYH mutation screening in the Netherlands should have detected this deletion in homozygous as well as heterozygous state, but until now the mutation has not been found there (by using sequencing amplicons for exons 1, 2, 3-5, 6-8, 9-11, 12-13, 14, 15 and 16, as described by Nielsen et al. 2005). Incompletely screened polyposis patient groups might be interesting to be tested for the large deletion.

Issues not for publication in the review report:

This reviewer is one of the MUTYH LOVD curators. Very recently, the same large deletion variant has been submitted to the MUTYH LOVD by another submitter than the authors of this manuscript (who also kindly submitted their case). However, due to delay in communication during holidays, this variant has not been made publically visible yet. It might be worthwhile to contact the other submitter via one of the LOVD curators, to exchange information.

Minor Essential Revisions:

(small adaptations to the text)

1. Background, First paragraph:
   1a: write “MutY” instead of “Mut Y”?
   1b: write “G:C to T:A transversions” instead of “G:C to T:A transversion”?

2. Background, Second paragraph: The last sentence “Mutations … APC 30% [7].” might suggest that MUTYH accounts for a larger proportion of polyposis patients than APC.

3. Background, Third paragraph:
   3a: “most pathogenic variants are missense … truncating mutations.” Suggestion to change this part of the sentence to e.g.: “most pathogenic variants are missense variants and only a minority consists of splice site and truncating variants.”
   3b: Although frequently called hotspots, p.Tyr179Cys and p.Gly396Asp are very likely to be founder variants (see e.g. ref 5 in the paper: Nielsen et al. 2010).

4. Case presentation, First paragraph: Starts with “A Brazilian female patient…” but later mentions “the patient stated that he…”.

5. Identification and characterization of the deletion, First paragraph: “Eleven primers pairs” should be “Eleven primer pairs”.

6. Identification and characterization of the deletion, Second paragraph: Why is “constitutive” in Italic?

7. Identification and characterization of the deletion, Third paragraph: “the deletion at 5’ of…” change into “the deletion at the 5’ end of…”?

8. Identification and characterization of the deletion, Fifth paragraph: “repetitive element is present on…” change into “repetitive element is present at” or
“repetitive element is present near”?

9. Identification and characterization of the deletion, Sixth paragraph:
9a: adapt the mutation nomenclature in accordance with the LOVD submission, c.348+33_*64+146del4285insTA or c.348+33_*64+146delinsTA.
9b: instead of “as a 2-nt” better use “as a 2-bp”?

10. Identification and characterization of the deletion, Seventh paragraph: mention that the AluY insertion is a polymorphic insertion?

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.