Author’s response to reviews

Title: Screening of the DNA mismatch repair genes MLH1, MSH2 and MSH6 in a Greek cohort of Lynch syndrome suspected families

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Author’s response to reviews: see over
Reviewer's report

Title: Screening of the DNA mismatch repair genes MLH1, MSH2 and MSH6 in a Greek cohort of Lynch syndrome suspected families

Version: 2 Date: 24 May 2010

Reviewer: Lovise Mæhle

Reviewer's report:

This is a manuscript which has been changed according to the advises given when I first reviewed it. The authors have done additional work and sequenced the third MMR-gene: MSH6. Interestingly they identified one family positive for a deleterious mutation in this gene. It is acceptable that the fourth gene PMS2 is not analysed, I agree that the possibility that they will find a mutation there is very low.

On page 9 under "Gene dosage alteration" the first sentence states: "The twelve families tested negative for point mutations......" Shouldn't the number be 11?

The reviewer is correct. The correction has been made accordingly.

And I still think that the authors try to make too much out of the one case of breast cancer in the F41 family with a MLH1 mutation. When they found that the woman did not carry the MLH1-mutation running in the family, they should only state that it is a case of breast cancer, either sporadic or caused by a gene not tested for here. If breast cancer is a part of Lynch syndrome, this case could be called a phenocopy. Breast cancer is found to be caused by MMR-mutations (detected by IHC-analysis) in a few single cases. But the life time risk of breast cancer is hardly increased in female MMR-mutation carriers.

The last sentence on page 12 has been rephrased to:"Both patients were genotyped and found not to harbor the particular pathogenic mutation, indicating that they were probably sporadic cancer cases. “

The statement in the last sentence on page 12: "This comes in contradiction with previous reports, where breast cancer was considered a phenotypic feature of Lynch syndrome's tumour spectrum" is not correct. The authors have only found that this breast cancer case is not caused by MMR-mutation. The finding is not in contradiction with previous reports, the only they can say is that they have not identified this case of breast cancer as a part of Lynch syndrome.

The whole sentence on pages 12 and 13 has been rephrased to meet the reviewer’s suggestion.
Reviewer's report

Title: Screening of the DNA mismatch repair genes MLH1, MSH2 and MSH6 in a Greek cohort of Lynch syndrome suspected families

Version: 2 Date: 27 April 2010

Reviewer: Ignacio I Blanco

Reviewer's report:

Authors have followed the main reviewer suggestions. However, they should clearly say that they were not able to study tumor samples. Microsatellite stability analysis and Immunohistochemistry are very important stabilshing an HNPCC analysis algorithm.

A sentence has been added on the discussion section (page 11, 1st paragraph) to highlight the fact that no tumor samples were available.

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

Quality of written English: Acceptable

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