Author's response to reviews

Title: Unusual presentation of Lynch Syndrome

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Author's response to reviews: see over
Response to reviewers’ comments.

Many thanks for your review. Please find attached the revised manuscript and our responses to the points raised as follows:

Reviewer 1:

Thank you for your comments on the pedigree which has been corrected to clarify cosegregation in this branch of the family.

We attach a table of additional data on the tumours from relatives in a distant branch of the family where all individuals in the table are known carriers. These data support the pathogenicity of the variant in that staining for the hMLH1 protein is lost in 8 cancers and an adenoma in six known mutation carriers. MSI testing in four cancers and one adenoma (from three individuals) showed high levels of instability.

The tumours tested in our branch of the family were the proband’s sarcoma and breast cancer as outlined in the text. The prostate and cervical cancer did not have staining undertaken. We recognise that we cannot state that these tumours are necessarily a result of mismatch repair. Our advice on prostate screening in our branch of the family is therefore based on the presence of two prostate cancers (in the proband and his brother) but we appreciate that it is difficult to know if this is applicable to the wider family.

We also agree that LOH data would potentially strengthen the case for pathogenicity but undertaking such studies is beyond the remit of this paper.

The issue of environmental factors is raised in relation to the proband’s father who was a non-drinker but did have a history of smoking.

Reviewer 2.

We have altered the risk range for colorectal cancer to reflect the variation in quotes and have altered the references accordingly.

The use of the word ‘synchronous’ was meant to refer to the fact that the proband had his sarcoma and his breast cancer diagnosed concurrently rather than implying that he had two sarcomas, so we have amended the manuscript to clarify this point.

Staining was not performed in the cervical cancer so we are not able to comment on whether this would have supported it having arisen due to mismatch repair.

Thank you for the comments on the paper by Nilbert which we have included.

We have amended the references and the legends.

We hope that you will find the revisions acceptable and look forward to your further comments.
With kind regards,

Dr Veronica Yu and Dr Sue Shanley