Author’s response to reviews

Title: Ubiquitous Neurocognitive Dysfunction in Familial Adenomatous Polyposis: Proof-of-Concept of the role of APC Protein in Neurocognitive Function.

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Author’s response to reviews:

Rodney John Scott, PhD, DSc
Hereditary Cancer in Clinical Practice

Dear Professor Scott:

We sincerely appreciate the review of our manuscript titled "Ubiquitous Neurocognitive Dysfunction in Familial Adenomatous Polyposis: Proof-of-Concept of the role of APC Protein in Neurocognitive Function (HCCP-D-19-00059)”. We are delighted to receive the news that our manuscript is potentially acceptable for publication in Hereditary Cancer in Clinical Practice, once we have carried out some essential revisions suggested by the reviewers.
We have reviewed the manuscript in accordance to the reviewers’ suggestions and hereby present a point-by-point response. We have used track changes to demonstrate all changes made to the original manuscript in response to the reviewers.

Reviewer #1:

1. “Genotype-phenotype correlation is overcalled in a study with such small numbers. Nor is this correlation exceptionally strong elsewhere in FAP. While there are correlations there are also significant exceptions.”

We agree with the reviewer that the number of patients in the study is small and thus our discussion on the genotype-phenotype correlation was modified within the context and limitations of the study, and known exceptions to the genotype-phenotype correlations. As such, we have modified the Abstract and Discussion section of the manuscript accordingly.

2. “Also overcalled is the conclusion that other germline hereditary cancer syndromes should be subject to similar study when the premise of this work revolves around the APC gene.”

We agree with the reviewer and have modified the manuscript accordingly in the Discussion session. Our original statement referred to examination of confounders associated with having a chronic illness.


Appreciate the additional reference recommended. We have included the new reference in the revised manuscript.

Reviewer #2:

1. “This paper looks into the neurocognitive function of FAP patients, showing that matched controls outperform individuals with germline APC mutations in several areas. Although there is some theoretical and animal study basis to expect cognitive dysfunction caused by lack of normal APC, there is hardly any literature on cognition in FAP patients available. I therefore appreciate the initiative to perform this study. Although the number of patients studied is relatively small, methods and statistics including multiple-testing correction are appropriate and the results, when confirmed by other studies, may help us to further support FAP families.”

We appreciate Reviewer 2 comments.

2. “One small comment: the authors wonder (page 18) whether the medical and psychosocial circumstances of having a (i.e. any) hereditary tumor syndrome can act as a confounder in studies on cognitive function. I agree, but I suggest that their examples of Lynch
and hereditary breast and ovarian cancer syndromes would not make the most ideal group to compare with FAP as these 2 syndromes start their surveillance and interventions ≥(20-25 yrs and not already in childhood as is the case for FAP. The authors could therefore 'refine' their remark a bit.”

We agree with the reviewer comment and have modified the manuscript accordingly. Please see response to Reviewer 1 above (item 2).

Thank you for the opportunity to review and resubmit the revised manuscript based on the reviewers suggestions. We believe this version fully address the concerns/comments made by reviewers and look forward to a favorable evaluation and acceptance for publication.

Respectfully,

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