Reviewer's report

Title: Polymorphisms in the mitochondrial oxidative phosphorylation chain genes as prognostic markers for colorectal cancer

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Reviewer: Sakari K Vanharanta

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In their study, Lascorz et al. investigate the association between genetic variants in a limited number of oxidative phosphorylation–related genes and colorectal cancer outcome. In general, the relationship between germline variants and disease outcomes is poorly understood and work at this front is needed. The sample set used here (613 cases with clinical follow-up) is substantial, and it is reasonable to think that it contains information on the genetic factors affecting CRC phenotypes. However, it is not clear that the kind of approach utilized here, cherry-picking genes of interest based on vague hints from gene expression studies, would be an efficient way to identify variants associated with CRC progression. Indeed, the results are non-conclusive.

There are several major points that limit the enthusiasm for this study:

1) The gene selection procedure is arbitrary, and it is not clear why only 7 genes were selected. Why not study the whole pathway? Also, many genetic variants associated with cancer have been identified in regions distant from the proximal promoter and coding regions. Why did the authors only focus on the promoter, 3', 5' and coding regions? It seems that a more unbiased effort with larger number of SNPs would be appropriate for this kind of work.

2) No correction for multiple hypothesis testing has been applied.

3) Is there an explanation for the fact that variants in different genes are associated with death, metastasis and tumor stage? Are these attributes unrelated in the data set used?

4) No model is provided that would even attempt to explain the observed associations between the genetic variants and tumor phenotypes. How do the T alleles in UQCRB 3'UTR confer protection from CRC death? How do the COX6B1 promoter/5'UTR variants promote metastasis? Are these SNPs the causative variants? These are difficult questions to answer, but especially when the genetic evidence is as weak as it is in this study, additional data would be essential before any conclusions can be drawn. An alternative approach would be to solidify the genetic findings.

Minor point:

1) On page 7, why do the authors state that rs7836698 is significantly associated with death due to CRC, when in fact the effect, if any, seems to be protective?
Level of interest: An article of limited interest

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:
I declare that I have no competing interests