Reviewer’s report

Title: A haplotype variant affecting the mitochondrial transportation of hMYH protein could be a risk factor for colorectal cancer in Chinese

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Reviewer: Pavel Vodicka

Reviewer’s report:

The manuscript by Chen et al. represents a potentially interesting contribution, consisting of two unequal parts: an experimental one, being stronger and a case-control study, posing substantial weaknesses. Given the number of investigated individuals, the study should be considered as a preliminary, pilot one. Additionally, there are several conclusions and/or summaries, which are not based on the generated data or the literature.

The comments will be listed below to assist the authors in preparation of the new, improved version.

Abstract:

The abstract generally needs a language correction (e.g. line 10 from the top-sentence is missing the verb).

A revision of the Methods part is necessary as the reader gets the impression that it is a simple case-control study, while at the end there is also a functional study on cell cultures.

The population included in the case-control study is not sufficient for this kind of study. Such a high OR and huge confidence intervals are doubtful considering the low frequency of variant alleles found.

The conclusions in the abstract are too strong and a bit speculative in light of the results.

Background part:

There are several editing mistakes and language problems which require appropriate revision for English (e.g. reference formatting, missing verb “been” in line 15, extensively instead of greatly, “which is“ may be omitted on p. 5, line 6, etc.).

Although mutations in hMYH are being identified in CRC cases, their link to CRC ethiology is unclear.

In general, there is not a proper use of the term "haplotype".

At the end of the first paragraph it is stated that "the biallelic germline mutations ......lead to the autosomal recessive colorectal adenomatous polyposis and cancer": this statement is not completely true because the mutations are not causative of CRC, they create a situation in the affected individual (extreme high
number of polyps) which increases the susceptibility to develop CRC.

The previous study cited (ref 10) is not correctly described in the text. Same problems may be observed for other studies (ref 11 and 12). It is not clear what the authors wanted to demonstrate by quoting ref. 12.

The connection between sporadic colorectal cancer (object of the present study) and FAP is not sufficiently clarified.

In the third paragraph it is assumed the same pathogenesis for both colon and rectal cancer, but there is scarce evidence for this.

First sentence of the 4th paragraph (In general, mutations…) has no meaning, please reshape it.

Page 5, lines 6 and 7: I wonder whether the authors did not rather mean genome „stability“ instead of „instability“.

The sentence „Increasing evidences have suggested that…“ is rather vague and needs focusing.

Last sentence on page 5: the aim of the study is not correctly clarified. There is an apparent overinterpretation, as a multistage process of colorectal cancer development was not investigated in relation to hMYH gene.

Methods part:

Obviously, the weakest part is the population characteristic, which lacks important information (e.g. age, sex, life-style, tumor localization or fundamental clinical data). I assume that the group of CRC patients (by the way, how the sporadicity was ensured?) and controls (not characterized at all) are insufficient in size for this kind of studies. There is a high risk of by-chance findings and bias!

Page 7, line 9: If the authors set up above methodology, it has to be provided by details. Otherwise a proper reference should be included.

Authors should have provided some details on the strenght of the statistics, carried out on 138 cases…

In this part there are few editing mistakes, such as: page 7, line 1 „nucleartide“, line 2 „preformed“, second para-should sound overnight.

Results part:

First paragraph: It is not clear, what kind of DNA was used for sequencing.

The population of controls was not tested for the Hardy-Weinberg equilibrium.

The variant allele frequencies represent very weak point in relation to the population size! CI ranging from 1 to 20 suggests high degree of randomness. The heterozygous variant configuration was discovered in about 4% of cases and 2% of controls (i.e. in 6 and 2 persons, respectively!), but none bore homozygous variant configuration! Considering such frequency, one wonders about the relevance for sporadic CRC. Surprisingly, out of 6 cases with the heterozygous variant configuration, 5 suffered from rectal cancer! Do the authors think that there is a same etiology for colon and rectal cancer? No hint about it was found
in Discussion.

Subcellular localization section: I would personally like to be provided with more unambiguous evidence for it (it may well be that I am not an expert in the particular area).

The last sentence of this section: apparently an exaggeration, as the excision repair function has not directly been investigated.

Random examples for language/editing problems: page 9, line 3: „exon 2“, page 9, line 8: „243 healthy controls“, page 9, line 9: „heterozygous“, page 9, line 19: „resulting in“, page 9, line 20: „was just“, page 9, line 23: „affected its“, page 10, line 6: „results previously“, page 10, line 8: „rather present both in“.

Discussion section:

First paragraph: It should be smoothed down. On the basis of the given results, I doubt whether the authors may claim the role of hMYH variant in CR carcinogenesis.

The discussion of the data (and their strength) on Chinese patients and controls is not sufficient.

It is not clear for the reader, what is the link between ROS in mitochondria and colorectal carcinogenesis. The same applies for the last sentence on page 13. At least more moderate expressions should be used.

Page 12, references should be cited: e.g. sentences ending on lines 10, 14 and 19.

Language editing: page 11, line 20: „have shown“, page 12, line 16: „influences“.

Conclusions:

They would require thorough rephrasing, as the presented data do not allow such conclusions. „Great“ contribution to colorectal carcinogenesis is based on the heterozygous variants, occurring in about 4% of (sporadic?) colorectal cases. What about the 96% of cases? By the way, the study on cell lines showed the effect of homozygous variant configuration, but these carriers have not been identified either in cases or in controls.

Tables section:

It is missing a table describing the population included in the study (number of cases and controls, distribution for sex, age average etc).

Table 2 presents some editing errors such as: „wild-type genotype“, „wild-type allele“, „variant allele“.

For consideration only: it maybe more clear for readers to have directly the description of genotypes (e.g. C/G for wild-type genotype, C/A or T/G for heterozygous genotypes, and T/A for variant genotype).
Level of interest: An article of importance in its field

Quality of written English: Not suitable for publication unless extensively edited

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

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