Reviewer's report

**Title:** Activating mutation in MET oncogene is inherited in familial colorectal cancer cases

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**Reviewer:** Annika A Lindblom

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This paper is a study of the MET oncogene in familial CRC. The study is performed in 163 subjects from 77 families and the results, a c.2975C>T variant, confirmed in tumor tissue from 299 additional CRC cases. The frequency of the variant is in this experiment more than twice the one published on dbSNP. It is suggested that this variant contributes to an increased risk of CRC as a tumor progression factor and recommend genetic testing.

The rational for the study is good. Methods well described (although it could be explained how MSI test was done) and relevant standards used.

Data is sound, however, the paper needs major revision. The presentation of the results is unclear as is the contents of table 1. Does the table 1 contain all known SNPs in CRC or what does it mean? – obviously it contains the gene variants mentioned as results but also many more – not mentioned. Some which seem to have been found in the study, silent variants and also one missense variant M362T, are not mentioned in the text? Two variants in the table, A320V and N375S seem not to have been detected in the study? Please clarify what is the content of table 1 (in the text and title of table). Please also make the text more clear what is the results. Now is said “The coding SNPs and their frequencies are listed in table 1, suggesting table 1 is the results of identified SNPs – but it is unclear since only three variants are discussed and two in the table is not result? When calculating population frequency only non-related cases should be used why in this study I suggest to use 4 c.2059 variants among 77 cases (if all families had at least one case) and thus the frequency become 5%. Also in the follow-up there was at least two cases who were related which means that one should calculate 8 variants among 198 cases (if the rest was non-related) and thus the frequency is 2.7%. It would also be good to, when first mention the T992I SNP to give both this name and c.2975C>T – now is used these names alternatively in the text and this is confusing.

The major problem with the paper is the recommendation of genetic testing. The results are interesting and if confirmed it could be implemented into the clinic. However, the study samples are both very small (77 and 298) and compared with dbSNP and the results cannot be considered conclusive but suggestive at best. Before implementing anything into a clinical setting this SNP needs to be tested in a large case-control study. Thus, this study should tone down the conclusions and remove the clinical context I think from discussion and abstract. In the
discussion it should be made clear the limitations of the study considering the sample sizes and lack of proper control material.

The title would be more correct to read: Activating mutation in MET oncogene in familial colorectal cancer.

Finally, it is a bit unclear also under conclusions: it is estimated (how?) that the specific variant is responsible for 4.5% of the 10% familial CRC. In introduction is said that 20% is familial and this is probably correct. Please clarify this – or rather leave it out since it may be better to estimate this when the actual frequency has been confirmed in a case control study.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**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.