Reviewer's report

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

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Reviewer: Ignacio I Blanco

Reviewer's report:

Neklason and Colleagues presented a very interesting paper entitled “Activating mutation in MET oncogene is inherited in familial colorectal cancer”.

Authors try to evaluate the possibility that germline changes in the MET gene may lead to colon cancer susceptibility in a familial setting. They scanned and sequenced all coding exons of MET in a sibling pair cohort. Authors report that MET p.T992I is present in the germline DNA of 4.7% of this cohort and this same change is confirmed in a second familial colon cancer cohort at a frequency of 4.2%. According with these results, Authors conclude that germline genetic testing for the MET c.2975C>T mutation will identify individuals who would benefit by frequent and early colon cancer screening.

Tyrosine kinases play a critical role in numerous cellular processes and the capacity for METR970C and METT992I to contribute to oncogenesis has been a topic of debate.

MET variants, R970C and T992I, have been found in lung cancer cell lines as well as individuals with lung, thyroid, renal, breast cancer, CLL, and lymphoma. Furthermore, different studies demonstrated that these sequence variants occur at similar frequencies among many different types of malignancy as well as in individuals without cancer. Tyner JW and colleagues (Cancer Res. 2010 August 1; 70(15): 6233–6237) suggest that these are rare single nucleotide polymorphisms not relevant to oncogenesis. Furthermore, Tyner JW and colleagues find no difference in transformative capacity or phosphorylation status of either variant compared with wild-type MET and suggest these alleles are not transforming. As we will comment later, the lack of a clear oncogenic role for these mutation make difficult their introduction in the clinical setting.

Nevertheless, this observation is in line with authors suggestion that the p.T992I mutation could functions as a progression factor rather than an initiation factor in the canonical colon cancer model.

In the present study, Neklason DW and Colleagues try to evaluate the possibility that germline changes in the MET gene may lead to colon cancer susceptibility in a familial setting. They scanned and sequenced all coding exons of MET in a sibling pair cohort of 169 siblings (148 affected with CRC and 21 unaffected). Authors report that MET p.T992I is present in the germline DNA of 4.7% of this cohort and this same change is confirmed in a second colon cancer cohort at a frequency of 4.2%. However, the second cohort included 130 cases without a
familial history. This cohort should be considered only a high risk cohort not a familial cancer cohort.

Neklason DW and Colleagues concluded that germline genetic testing for the MET c.2975C>T mutation will identify individuals who would benefit by frequent and early colon cancer screening. However, the lack of confirmation of the associated cancer risks in a large series and the fact that p.T992I mutation is not tissue-specific make difficult to introduce its determination in the clinical setting.

Major Compulsory Revisions:
1. Authors considered the second cohort as a familial cancer cohort. However, the second cohort included 130 cases without a familial history. For this reason, this cohort should not be considered a familial cancer cohort. It should be considered only a high risk cohort.
2. There are not enough evidences to confirm that the p.T992I mutation is a colorectal cancer high risk mutation. Authors’ results should be confirmed in a large series of both colorectal cancer patients and non cancer individuals.
3. The lack of confirmation of the associated cancer risk in a large series and the fact that p.T992I mutation is not tissue-specific makes difficult to introduce its determination in the clinical setting. It is almost impossible to perform a correct genetic counseling process without having a complete picture of the cancer associated risks. The p.T992I mutation could act only as a modifier risk mutations and a negative result did not allow modifying the screening protocol based on personal or family history. For these reasons, although germline genetic testing for the MET c.2975C>T mutation could identify individuals who would benefit by frequent and early colon cancer screening more data are needed before making a general recommendation.

**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