Reviewer’s report

Title: ARLTS1 polymorphism is associated with an increased risk of familial cancer: evidence from a meta-analysis

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Reviewer: Bente Talseth-Palmer

Reviewer's report:

This is a meta-analysis of 5 SNPs in the ARLTS1 gene (official gene name is ARL11 - should this be used or at least referred to?), which has found a significant association of one SNP (Cys148Arg) with both sporadic and familial cancer risk. And therefore claim that this gene should be considered as an important potential target for personalized medicine in cancer treatment.

It is a well conducted study that has followed the "checklist for meta-analysis" published by M.W.Russo (Gastroenterol. Hepatol, 2007). An OR of 1.36 for sporadic and 1.26 for familial cancer risk was shown for Cys148Arg SNP and I am wondering how they interpret the risk to be high enough for it to be a potential target for personalized medicine?

I am not a statistician and therefore I am not commenting on statistical methods used. But I do have one "statistical" question; SNPs are subject to the same multiple testing issues in meta-analysis as in single sample studies, but this has not been adjusted for or discussed (i.e. Bonferroni correction).

Major essential revisions

* In addition to refer to SNPs as Cys148Arg, also include C148R and rs numbers which is mostly used for SNPs today. Maybe make a table showing all the different names of the 5 SNPs (polymorphisms)

* In result section; can be summarized by writing the following at the end of the 1st paragraph in results:

  o Not all studies genotyped all SNPs included in this meta-analysis, therefore number of included studies will differ between the SNPs. All results will be presented like this: OR (95% CI), p-value.
By doing this you can write results as this in next paragraph; …pooled into the meta-analysis (CC vs. TT: 1.27 (1.15-1.41), p=0.000 Fig2; CC + TC vs. TT: 1.13 (1.02-1.27), p=0.026, etc.) = much easier to follow.

P-values in a lot of the result in section Cys148Arg is missing in the paragraph.

* In section Trp149Stop, Por131Leu….. it says: Overall, significant main effects on cancer risk…. But the results are not significant (p=0.700 and p=0.635). In Table 4 though the results in that section says p=0.001 for both. Which is correct? In the same section all results show the same, so can be shortened to say: No significant results are observed for and of these SNPs and refer to table 4. No need to repeat the same thing for each SNP and all the numbers are in the table.

* In Discussion (line 30-35) you write; "Yet, it did not mean that other variant have no association with cancer. These variants may be with minor effects individually, but they are likely to contribute adequately in combination to lead the failure of immune response". Why have you come to this conclusion as there is no indication at all that they contribute towards cancer development? I can understand this reasoning if you saw a trend towards an association but not without.

* In Discussion (line 53-59);"… it is outstanding that this study is the first time to manifest the association between these five SNPs and cancer risk. Also our research provides powerful evidence for future large scale population-based cohort study and case-control study". First of all you did not find an association between 5 SNPs and cancer risk, just one of them and secondly, I am not sure you can say the study provides powerful evidence for future large scale population-based cohort study and case-control study from the findings you present.

* Conclusion - one of your major findings is that you have excluded the association of any of the other 4 SNPs with cancer risk. This should be included in the conclusion.

* English grammar needs attention.

* Discussion p.2 (line 3-5); ".…..reduction or absence of ARLTS1 expression contributes to DNA mutation with LOH in breast cancer (23) - this article does not talk about ARLTS1 expression, DNA mutations with LOH in breast cancer. Make sure you reference correctly. Same goes for next sentence and reference 7 (does not say methylation in thyroid cancer). Go through all references and make sure you are saying what you are referencing!
Minor Essential Revisions

* Introduction p.2 (line 1-2); "..... which was published in the New England journal (2)" - no need to state the journal when you are referencing and if you do use the correct name New England Journal of Medicine.

* Introduction p.2 (line 8-9); "However, to update the results of these studies have remained inconsistent". What do you mean here? Sentence does not make sense.

* M & M p.1 (line 21-22); suggest changing sentence to "Database searches of Medline, PubMed, Embase, Web of Science and China National Knowledge Infrastructure (CNKI) were performed. If you need to pub in timeline - you might want to justify why you have chosen to start in 2005.

* It is normal to refer to SNPs with rs numbers today, maybe a table with Cys148Arg, C148R, genotype and the SNPs rs number would be a good idea?

* M&M p.1 (line 61); "... were extracted from each study; ..... ethnicity, study design. Might be a good idea to say "ethnicity of study population".

* M&M p.2 (line 2); "Different cancer types were was classified..." Can't use were was - choose the correct one.

* M&M p.2 (first line in Quality assessment) is hard to read - suggest changing to "The quality of the included publications was assessed according to a quality assessment scale (Table 1), which was modified from previously published meta-analysis (8-10). In the next sentence, delete word: severally.

* M&M p.2 (line48); "ARLTS1 polymorphism and cancer risk" should read "ARLTS! Polymorphisms and cancer risk".

* M&M p.2 (line 51); ".... and studies quality." should read "... and study quality".

* M&M p.3 (line 5); change the work ".... Besides Egger's test" to ".... in addition Egger's test".

* Add references in Table 2 (behind Author names)

* Results p.1 (line 11); You are referring to 10 articles meeting the inclusion criteria, but up until now you have talked about included studies. Change articles to studies in next two
sentences. Same paragraph; line 15 - add "ss" to polymorphism as you are referring to more than one.

* Results p.1 (line 26-27) - suggest changing to; "..... 11 studies were included in the meta-analysis for SNP C148R with 7,152 cases and 6,698 controls."

* Results p.1 (line 35): change "…was listed in Table 3" to "….are listed in Table 3".

* Results p.1 (line 37-38) - English grammar: "controls source" should be "control source" x 2, "studies quality" should be "study quality". "CC polymorphism" should be "CC genotype" + add studies behind population-based and hospital based in the next sentence.

* Results p.1 (line 43) - suggest changing sentence to; "For study quality, the significant results only existed in high quality studies….". Also in line 48 you refer to significant results as positive results.

* Table 3 - write ARLTS1 genotype before CC vs. TT, etc.

* Discussion p.1 (line 48); change "incompletely clear" to "unclear". Also not possible to follow thought when saying …' unclear such as pathways, …". What do you mean here? That we don't know what pathways the gene work in? Need to make this clearer. Next sentence starts with "The possible mechanism is that…" Mechanism of what?

* Discussion p. 1 (line 53-56) - English grammar; delete the work "on" before acceptors, change "become" to "becoming" and write "the ARLTS1 gene".

* Discussion p.2 (line 7-14 - English grammar; say "immune responses resulting in…", add "s" to polymorphism x 2 (when you talk about more than 1 SNP).

* Discussion p.2 (line 46); "…. some had benign disease." - like what?

* Discussion p.2 (line 53-54): "outstanding that this study is the first time to manifest" - you are not the first study to associate the 5 SNPs and cancer risk (and you only found association in 1 SNP!), you can say first meta-analysis.

* Discussion p.2 (line 56-59); "Also our research provides powerful evidence for future large scale population-based cohort study and case-control study." Why?

* Declarations: You have 2 Authors' contribution - combine it to 1.
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An article whose findings are important to those with closely related research interests

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Please indicate the quality of language in the manuscript:

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