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ESPS Peer-review Report
Name of Journal: World Journal of Gastroenterology
ESPS Manuscript NO: 6073
Title: New genes emerging for colorectal cancer predisposition
Reviewer code: 02533481
Science editor: Qi, Yuan
Date sent for review: 2013-10-01 20:42
Date reviewed: 2013-10-30 04:56

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A (Excellent)	[ ] Grade A: Priority Publishing	Google Search:	[ ] Accept
[ ] Grade B (Very good)	[Y] Grade B: minor language polishing	[ ] Existed	[ ] High priority for publication
[Y] Grade C (Good)	[ ] Grade C: a great deal of language polishing	[ ] No records	
[ ] Grade D (Fair)		BPG Search:	[ ]Rejection
[ ] Grade E (Poor)	[ ] Grade D: rejected	[ ] Existed	[ ] Minor revision
		[ ] No records	[Y] Major revision

COMMENTS TO AUTHORS

The authors present a review paper on new genes emerging for colorectal cancer (CRC) redisposition, with focus on new sequencing technologies. This is an important topic of its field. ne main finding is related to germline mutations in the POLE and POLD1 genes responsible for a new form of predisposition called polymerase proofreading-associated polyposis. It is to be noted that this has partly been highlighted in literature elsewhere (Seshagiri 2013). The authors spend time on reviewing how next generation sequencing (NGS) technologies may be used to reveal germline variations predisposing CRC. There is a separate paragraph on how individuals should be selected for this analysis, although this seems to be related to hereditary CRC cases only. Of the NGS studies that are presented in the manuscript, the study designs are different and as such patients have been selected differently. For instance the study by Palles et al. included patients with a positive history of CRC, whereas the study by Smith et al. included unrelated patients with sporadic CRC. When presenting the CDCV hypothesis, this can also be seen as an effort to explain genetic susceptibility of sporadic CRC. Thus, when reading the manuscript it is not clear to the reader if the focus is on hereditary, familial and/or sporadic CRC. This review paper should make this clear, and further discuss implications of the different study designs related to the inclusion of patients with or without a family history of CRC. In conclusion, the manuscript should be re-structured and formatted to make it more concise, to the point and easy to read. There are also several typographic errors in the manuscript, some of which are mentioned below.

Some Specific Comments
Introduction

- Page 5, 1st paragraph: I suggest estimates are presented with less significant figures, for instance 473,258 could be presented as approximately 473,200.
- Page 5, 1st paragraph: Incidence rates are compared across the world without a comment on the quality variations in cancer registries.
- Page 5, 2nd paragraph: There is a repetition of the prevalence from the 1st paragraph:
"The lifetime risk of CRC in the general population is about 5-6 % in Western countries.." vs "Approximately 5 % of the population develops..". This figure should
be stated consistently.
Hereditary CRC
- Page 8, 3rd paragraph: "Most patients have a family history of colorectal polyps and
cancer, but de novo APC mutations are responsible for approximately 25 % of cases".
This lacks a reference in the manuscript.
- Clinical literature such as UpToDate (accessed October 2013) often speaks of familial adenomatosus polyposis (FAP) and MYH-associated polyposis (MAP) as two separate
entities caused by different germline mutations, although their clinical spectrum might overlap. I therefore suggest that there is a separate paragraph on MAP. Furthermore I suggest Table 1 to be altered accordingly so that the syndromes FAP and MAP are separated.
Approaches to identify genetic variants for CRC risk
- Page 9, 3rd paragraph: Typographic error "common disease-common variant". Overview of new sequencing technologies - Is this section the focus of the paper? It should be re-organized somewhat because it both discusses the selection of patients (pre-analytical), sequencing methods and filtering processes (analytical) and validation of candidate variants (post-analytical) in an unorganized fashion.- I suggest creating a figure illustrating the step-wise process including important preanalytical, analytical and post-analytical steps.- In general pages 10 – 12 would benefit from more references.
- Page 10, 2nd paragraph: "Due to recent technology and variant calling algorithm improvements, NGS is probably nowadays more accurate than Sanger sequencing".
This lacks a reference in the manuscript. - Page 11, 3rd paragraph: "…which allows sequencing a larger number of samples with better accuracy". How do you define the term accuracy in this context?

- Page 11, 4th paragraph: This paragraph is discussing selection of patients (preanalytical) and is obviously a critical step in the design of such studies. This part could
be presented first in this section. In addition it only describes the inclusion of patients
with a positive CRC history. It also lacks considerations regarding the number of
patients needed in order to find given genetic variations (i.e. the power).
- Page 11, sub-section "Data filtering and prioritization in NGS": Why selecting a
coverage threshold of 10 x - is there any literature supporting this notion?
- Page 13, 8th paragraph: Sanger sequencing is only one of several possibilities for lowthroughput sequencing validation.

New genes identified for CRC genetic predisposition

- This section refers to the results of both low-throughput sequencing and highthroughput sequencing studies, and is initially not clear to the reader.

Figures/Tables

- Figure 1: Incorrect reference name in figure legend:

"(data adapted from Ferlay et al. [1].)"

- Table 1: Lacks reference in table legend.
- Table 2: Lacks reference in table legend.

References

Seshagiri S. Nat Genet. 2013 Feb;45(2):121-2. doi: 10.1038/ng.2540.

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[ ] Grade A (Excellent)	[Y] Grade A: Priority Publishing	Google Search:	[ ] Accept
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[ ] Grade C (Good)	[ ] Grade C: a great deal of language polishing	[ ] No records	[ ]Rejection
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[ ] Grade E (Poor)		[ ] Existed	[ ] Major revision
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COMMENTS TO AUTHORS

The manuscript deals with the description of new genes that may increase the risk of developing a CRC. It is well written and references are much updated. The core of the manuscript seems to be a description of new sequencing technologies and their applicability on the search of new CRC predisposition genes. However, the general structure of the manuscript seems a little confusing to the reader. It begins focusing on hereditary syndromes and then jumps to the new sequencing technologies, when following the text these technologies seem to be applied mainly to familial CRCs. The authors comment on the election of individuals for sequencing on page 11, addressing the importance of choosing families with stronger familial aggregation, but the published reports on this topic include both sporadic and familial cases. Perhaps a more specific description of selection of individuals for sequencing and its influence on the results of the studies should clarify the practical relevance of these findings. As a general review on new candidate genes, and from a non-genetist reader point of view, I would like some comment on what should be the next step to elucidate the pathogenic role of these genes. We are overwhelmed with hundreds of putative genes but most of them may not be real driver genes. How should we deal with all this information from a translational perspective?. Finally some typographic mistakes: - Page 8, coutaneous, sebaceous - Page 9, common disease-common variant

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COMMENTS TO AUTHORS

This was a good review article for the general clinician with no previous in depth knowledge of genetics. The review gives an important overview on the genetic methods and pros and cons of next gen, whole genome versus exome sequencing. Although many of the findings discussed in this article are not particularly new or novel, the provide a sound background for the general reader. Perhaps the article should have a larger focus on NEW findings in CRC genetics. Major suggestions Final section Expand on the functional role of POLE and POLD-1 i.e. polymerase proofreading genes. Has any other functional ex- or in vivo work been done on these genes? Table 1 - could the functions of the genes included be another column of this table i.e. tumour suppressor gene, mismatch repair gene, unknown etc... Minor suggestions Sentence 4 of the abstract (also appears in core tip)starting "Therefore, there is..." needs to be revised as it makes little sense Sentence 3 of the introduction change "For 2015" to "In 2015" More references are required for the introduction as there are many unreferenced comments/evidence/statistics In the para regarding Lynch syndrome - The epigenetic aspects are interesting and should be expanded upon Please expand on the Amsterdam criteria (perhaps as a figure or table if nessesary) First sentence page 10 - change nonsyndromic to non-syndromic? Sentence one of page 11 'de novo' instead of 'the novo' Final sentence of para 2 of page 11, "different systematic error associated , as conventional Sanger sequencing, which increases the costs and time of the analysis." insert such after comma. Page 13 expand abbreviation SNV When discussing FAP - what about peri-ampullary tumours?