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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 39924

Title: *FANCA* D1359Y mutation in a patient with gastric polyposis and cancer susceptibility: A case report and review of literature

Reviewer's code: 02679280

Reviewer's country: Reviewer_Country

Science editor: Ze-Mao Gong

Date sent for review: 2018-05-22

Date reviewed: 2018-05-22

Review time: 6 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	[ ] Accept (High priority)	Peer-Review:
[ ] Grade B: Very good	[Y] Grade B: Minor language polishing	[ ] Accept (General priority)	[Y] Anonymous
[Y] Grade C: Good	[ ] Grade C: A great deal of language polishing	[Y] Minor revision	[ ] Onymous
[ ] Grade D: Fair	[ ] Grade D: Rejection	[ ] Major revision	Peer-reviewer's expertise on the topic of the manuscript:
[ ] Grade E: Do not publish		[ ] Rejection	[ ] Advanced
			[Y] General
			[ ] No expertise
			Conflicts-of-Interest:
			[ ] Yes
			[Y] No

SPECIFIC COMMENTS TO AUTHORS

Comments to Authors This manuscript is a case report on gene-panel sequencing of benign and gastric polyps of one patient. As a result, it describes three germline mutations (BAI3 p.S311W, FANCA pD1359Y, RPS6KA2 p.T595I) and various somatic

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mutations. In general, the manuscript is well-written, and reports a patient with gastric polyposis and cancer susceptibility, and with a FANCA gene mutation. Major points Material and methods p11. Please, provide at least the following information regarding the gene-panel sequencing: what is the size of the target, how much of the captured region is covered by at least 25 reads that authors used as a threshold for filtering, what was the mean coverage for the samples (including minimum and maximum). Please, provide more details for the variant filtering: were all SNVs included or were these further filtered based on their effect (synonymous/non-synonymous, splicing etc.)? Were any predictions made for the effect of the amino acid alterations (PolyPhen, SIFT, MutationTaster etc.)? Tables Table 1. Please provide the overall read depth for variants having less than 10% frequency in the samples. As C to T conversion is common artefact of FFPE samples, how authors excluded the possibility that these (particularly the ones observed only in one sample) do not represent artefacts? Minor points Introduction p8. The phrase "genetic expression profiles" is misleading, the expression referring traditionally to RNA as a starting material. "Genetic profile" or "mutational profile" would be more suitable given the analysis done. Results p.11 Was samples from other organ sites (e.g. blood, buccal swab) available to further confirm the germline origin of the three observed mutations? Discussion p.14 It would be good to mention that this FANCA D1359Y mutation has previously been described in the context of FA. p.15 I do not quite follow, how this sentence "In the past, to identify a subtype of FA needed clinical awareness and was often hampered by labor intensive conventional molecular diagnosis tools such as conventional mutation analysis, gene transfer studies or western blotting" relates to the current case report. I would recommend omitting this. Tables Table 2. How does this relate to the manuscript? It is not referred in the text.

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 39924

Title: *FANCA* D1359Y mutation in a patient with gastric polyposis and cancer susceptibility: A case report and review of literature

Reviewer's code: 02535507

Reviewer's country: Italy

Science editor: Ze-Mao Gong

Date sent for review: 2018-06-14

Date reviewed: 2018-06-14

Review time: 0 Hour

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection	Peer-Review: [Y] Anonymous [ ] Onymous Peer-reviewer's expertise on the topic of the manuscript: [ ] Advanced [Y] General [ ] No expertise Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

An excellent genetic study about gastric cancer. Some points are unclear for me: a. Why gastric polyps were not removed, but only subjected to biopsy at the first episode of bleeding? b. There is a link between gastric hyperplastic polyp evolution to carcinoma

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and duodenal GIST development? c. It seems that surgery induced a sustained remission of anemia, bleeding and tumor development. In this case I cannot understand why the source of bleeding was not removed at the first episode.

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 39924

Title: *FANCA* D1359Y mutation in a patient with gastric polyposis and cancer susceptibility: A case report and review of literature

Reviewer's code: 03017407

Reviewer's country: Reviewer_Country

Science editor: Ze-Mao Gong

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SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	[ ] Accept (High priority)	Peer-Review:
[ ] Grade B: Very good	[ ] Grade B: Minor language polishing	[ ] Accept (General priority)	[Y] Anonymous
[ ] Grade C: Good	[Y] Grade C: A great deal of language polishing	[ ] Minor revision	[ ] Onymous
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[ ] Grade E: Do not publish		[ ] Rejection	[Y] Advanced
			[ ] General
			[ ] No expertise
			Conflicts-of-Interest:
			[ ] Yes
			[Y] No

SPECIFIC COMMENTS TO AUTHORS

Theoretically, this is an interesting case. However, all along the paper, there is a tremendous confusion between germline and somatic variants (mutations). Germline mutations can predispose to cancer and this is the case of monoallelic mutations of FA

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genes. If mutations are low/medium penetrant, family history of cancer can be absent and, consequently, the mutation carrier affected with cancer will appear as a sporadic case. Somatic mutations are only present in pre-neoplastic and neoplastic lesions and are associated with cancer progression. Which is the evidence that the identified mutation is germline, i.e. present in normal tissues? The authors extracted DNA "from benign gastric polyp, gastric adenocarcinoma and jejunal GIST tumor". No constitutive DNA from normal tissue was analyzed? If constitutive DNA was not extracted from blood but from FFPE sections, how areas with normal cells were selected? The sentence "Massively parallel sequencing for a panel of 409 cancer-related genes in these tumors identified 3 germline mutations (BAI3 p.S311W, FANCA pD1359Y, RPS6KA2 p.T595I) and 12 somatic mutations in 3 benign and 3 malignant tumors" is quite confusing. Assuming the presence of a germline mutation in FA gene, is a second hit in the same gene present in tumor cells? Again, about confusion between germline and somatic variants: the sentence "It was reported that patients with a monoallelic FA gene mutation are also prone to the development of colorectal cancer when an additional second hit, such as MHL gene mutation is present" is totally inappropriate. The mentioned paper (Xie et al. 2010) evaluates the functional effect of a germline mutation in MLH1 (not in FANCJ), which is a MMR gene associated with the Lynch syndrome. The MLH1 mutation was shown to impair the binding between MLH1 and FANCJ proteins, thus impairing the MMR signaling. These are just example: as I said, there is confusion all along the paper between germline (predisposition) and somatic (carcinogenic process) events. Accordingly, the paper has to be completely re-written.

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 39924

Title: *FANCA* D1359Y mutation in a patient with gastric polyposis and cancer susceptibility: A case report and review of literature

Reviewer's code: 01214406

Reviewer's country: India

Science editor: Ze-Mao Gong

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Review time: 2 Days

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	[ ] Accept (High priority)	Peer-Review:
[Y] Grade B: Very good	[Y] Grade B: Minor language polishing	[Y] Accept (General priority)	[Y] Anonymous
[ ] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] Minor revision	[ ] Onymous
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[ ] Grade E: Do not publish		[ ] Rejection	[ ] Advanced
			[Y] General
			[ ] No expertise
			Conflicts-of-Interest:
			[ ] Yes
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SPECIFIC COMMENTS TO AUTHORS

this is a good case report with a followup of long duration showing sequential mutational changes from benign polyp to adenocarcinoma in stomach. the study clearly shows that like adenocarcinoma colon gastric adenocarcinoma may also follow the

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adenoma carcinoma sequence authors have done detailed mutational analysis of followup biopsies to prove above hypotheses but a single case is not enough to make any final conclusion. Results are clear but should be made more concise. discussion is too long,the authors should mainly concentrate on significant mutational changes that support sequential adenoma carcinoma sequence Language and formatting needs improvement

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