Peer Review File

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I. Reviewer A

Thank you very much for the careful reviews of the Reviewer A. We corrected several points according to the descriptions by the reviewer, as described below. We indicated the changes point by point and highlighted them in the revised paper.

Comment #1: Please elaborate on the clinical significance of the point mutation in c.192A>G? What effect does this mutation have at the protein level and how is this implicated in GAPPS?

Reply #1: There are two promotor lesions, 1A and 1B, in *APC* gene (Front Oncol. 2021;11:653222. doi: 10.3389/fonc.2021.653222. eCollection 2021). *APC* promotor 1A is physiologically hypermethylated at proximal gastric mucosa (Best Pract Res Clin Gastroenterol. 2021;50-51:101728). The point mutation in c.-192A>G of *APC* gene reduces the binding of the transcription factor Yin Yang 1, resulting in the decreased transcription activity of *APC* promotor 1B (Oncogene. 2011;30(50):4977-89). Therefore, the germline mutation at c.-192A>G of *APC* promotor 1B in GAPPS suppress the transcription of *APC* gene by the dysfunction of *APC* promotor 1A and 1B at the proximal gastric mucosa, which resulted in the decrease of APC protein at the proximal gastric mucosa. These findings might explain one of the mechanisms responsible for the development of multiple polyps at the proximal gastric lesions in GAPPS. **(on page 8 line 10-18)**

Changes in the text: **on page 8 line 10-18.**

Comment #2: Authors describe case 1 as "followed up with regular EGD and biopsy," at what interval are these patients surveilled with endoscopy? How many biopsies were collected? On surveillance endoscopy, were there any grossly abnormal mucosal findings in addition to polyps (i.e. ulceration, erythema, pale areas) that may be suspicious for malignancy and prompt recommendation for gastrectomy over continued endoscopic surveillance?

Reply #2: Case 1 was followed up with regular EGD every year, and two to five biopsies were collected in each endoscopy. The endoscopic findings showed an increase number of polyps but histologically no abnormal findings by biopsy. **(on page 5 line 4-6, on page 5 line 9-11, Figure 1B, Figure legends)**

Changes in the text: **on page 5 line 4-6**

Comment #3: On line 89 authors state case 3 was histologically diagnosed with gastric adenocarcinoma on gastrectomy, however, endoscopic biopsy showed tubular adenoma. Is this an expected finding? Please elaborate on the efficacy and safety of endoscopic surveillance and the false negative biopsy rate in GAPPS. What were the histological findings on the remaining two individuals that underwent gastrectomy (case 1 & 2)?

Reply #3: tubular adenoma.

The regular EGD of Case 3 showed polyposis with no malignancy by sampling biopsy, while the resected stomach by gastrectomy showed adenocarcinoma lesion in some polyps. This malignant diagnose after surgery was an expected finding. Prophylactic

gastrectomy was performed in case 3 because polys of GAPPS have high risk of gastric adenocarcinoma even if the biopsies of some polyps show no malignancy. A total of 112 GAPPS cases underwent prophylactic gastrectomy in the literature, and seven of 112 cases showed gastric adenocarcinoma after gastrectomy while preoperative examination of polyps showed no adenocarcinoma. Postoperative histopathologic findings of Case 1 and 2 showed no malignancy. **(on page 5 line 18-19, page 8 line 7-9)**
Changes in the text: **on page 8 line 7-9.**

Comment #4: For Figure 1, case 3 is histologic data available that coincides with the representative endoscopy image?
Reply #4: In figure 1B, histologic picture of case 3 was not available, but we added histologic findings that coincides with the endoscopy image in figure 1B legend, as follows. In case 3, macroscopic finding of EGD suggesting dysplasia, and histologically diagnosed as tubular adenoma. **(on page 5 line 18-19, Figure 1B, Figure legends)**
Changes in the text: **Figure legends**.

Comment #5: In the discussion the authors state "Our cases showed that both FGPs and c.192A>G mutations at the germline level were present in all seven cases examined" however, lines 86-87 state that "germline mutation analysis of APC promoter 1B region was not performed" in case 6, please clarify.
Reply #5: We correct the exact number of cases who were performed the germline mutation analysis of *APC* promoter 1B region.
Changes in the text: **on page 7 line 4.**

Comment #6: The authors state prevalence of FGPs was 58.9% on line 107, however, this estimate may be incorrect given a significant amount of family history data is missing from Table 1 (data from 11 families not reported). Please clarify.
Reply #6: As the Reviewer pointed out, the exact number of family members in 11 families was unknown. We recalculate the prevalence of GAPPS from 24 measurable families. **(on page 7 line 6, Table I)**
Changes in the text: **Table I.**

Comment #7: The authors suggest patients with GAPPS may have "rapid progression" of disease on line 118, however, there is limited evidence to support this. In fact, it is reported that the proband in family 33 was diagnosed in his 30s and lacks gastric adenocarcinoma on endoscopic biopsy over 40 years later. Additionally, the authors cite family 9 as having "rapid progression of primary GC" in lines 123-124. How does family 9 compare to families 33 and 34 investigated in this study?
Reply #7: We described the background of family #9 in more detail, and added information of family #24, as follows. In family #9, the patient showed dysplasia and liver metastases 5 years, despite the continuous surveillance EGD was performed every 18- to 24-month intervals (Gastrointest Endosc. 2016;84:718-25). In family #24, two patients underwent surveillance EGD every 3 month, and they were diagnosed gastric adenocarcinoma one year after initial EGD (Clin J Gastroenterol. 2021;14:92-7). Based on these findings, we commented in the discussion, as follows. GAPPS might show rapid malignant progression of gastric polyps in compared with the common gastric polyps. **(on page 7 line 25, on page 8 line 1-4)**

Changes in the text: **on page 7 line 25, on page 8 line 1-4.**

Comment #8: Please specify which patients underwent prophylactic total gastrectomy without malignancy or dysplasia in lines 121-122.

Reply #8: We specified patients underwent prophylactic total gastrectomy without malignancy or dysplasia in the discussion, as follows. In 112 cases with fundic gland polyposis, 21 cases without dysplasia or cancer underwent prophylactic gastrectomy, and 7 cases showed cancer or dysplasia after gastrectomy. **(on page 8 line 7-9)**

Changes in the text: **on page 8 line 7-9.**

Comment #9: Please rephrase your terminology regarding disease penetrance in lines 106-108.

Reply #9: We rephrase “penetrance” or “penetration” to “morbidity rate”. **(on page 7 line 5-7)**

Changes in the text: **on page 7 line 5-7.**

Comment #10: The authors state standard guidelines remain to be established. Please elaborate on the current state of clinical management of GAPPS and cite any efforts that have been taken to develop protocolized management of these patients.

Reply #10: We summarized the clinical management of GAPPS as resemble as Reply #7. Considering the family #9 and #24 which had gastric cancer during regular follow-up, it is controversy that how long follow-up interval would be the best. Tacheci I, *et al*. suggested prophylactic gastrectomy between 30 and 35 years of age or five years earlier than the age at which the youngest family member had gastric adenocarcinoma (Best Pract Res Clin Gastroenterol. 2021;50-51:101728.). And about EGD, Foretová L, *et al*. suggested that patients undergo EGD every 6 months if prophylactic gastrectomy is refused (Klin Onkol. 2019;32(Supplementum2):109-17.). Based on previous reports and our cases, we recommended that the surveillance EGD for GAPPS patient might be performed every 6 months. **(on page 7 line 23-25, on page 8 line 1-4, on page 8 line 6-7)**

Changes in the text: **on page 7 line 25, on page 8 line 1-4, on page 8 line 6-7)**

II. Reviewer B

Thank you very much for the careful reviews of the Reviewer B. We correct several points according to the descriptions by the reviewer, as described below. We indicate the changes point by point and highlighted them in the revised paper.

Comment #1: Table I may be revised to have a column "Patients with GC/ all family members" instead of "Number of patients with GC in family" to be more precise.

Reply #1: As the Reviewer recommended, we corrected the title of the column and number in Table I. Also, we clarified the parameter as the number of all examined family members. **(on Table I)**

Changes in the text: **on Table I.**

Comment #2: It is not clear enough why FGPs cases/ all family members are shown as "6/6" and "1/1" in #33 and #34. Adding some notes to indicate that "N.E. (not

evaluated) in Figure 1 and 2 were not counted in all family members to calculate the FGPs cases/ all family members" is preferable.

Reply #2: We added the note in Table I, as follows. *, Not evaluated cases in Figure 1A and 2A were not counted in all family members. **(on Table I)**

Changes in the text: **on Table I.**