Author’s response to reviews

Title: Chinese siblings with hereditary medullary thyroid carcinoma caused by RET mutation: implications for RET oncogene detection

Authors:

Qin Huang (260425551@qq.com)
Aihua Hu (964599425@qq.com)
Mingsheng Zhang (zms75@163.com)

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Author’s response to reviews:

Reviewer 1

The presented cases seem original, but all the manuscript should be re-written with extensive English revision.

The clinical presentation of the two brothers should be described in a more schematic way, starting from the history up to clinical examination and outcomes.

RE: Thanks for your suggestions. We had revised the clinical presentation section in a more schematic way. The details please read the revised manuscript.

In addition to genetic, imaging and histological findings, it would be interesting to view results of biochemical assessment, including concentrations of calcitonin (even with serial measurements) and other biomarkers (such as PTH, catecholamines, etc.). Biochemical data could be summarized in a table, including also values from the other family members, when available.

RE: Thanks for your meaningful suggestions that help to perfect our manuscript. We had added the pre- and post-surgery levels of CEA, Ctn and PTH in Table 1. The values from one family member was also included.

Minor point: do not use "euthyrox" instead of the pharmacological principle.

RE: We had use “thyroid hormone” instead of "euthyrox".

Reviewer 2
General comments to the authors:

Authors described the two cases with familial medullary thyroid carcinoma caused by p.C620Y mutation in RET oncogene. This is a first report of Chinese, although the mutation is a common mutation in the world. Because the patients with this mutation show wide range prognosis as shown in this report, physicians cannot conclude the handling of this case. Further case studies and investigations are required to evaluate significance of occult p.C620Y RET oncogene mutations on the prognosis.

Authors described important practical issues. However, revision of the manuscript is required to clarify the intended meaning and to realize what physicians should remind from this manuscript. In addition, authors clarify and generalize what is the clinical importance in this manuscript that described first case series in China. These revisions can make this article more comprehensive and attractive for the readers in this journal.

RE: Thanks for your meaningful suggestions that help to perfect our manuscript. We had revised our manuscript to emphasize of the importance of RET oncogene mutation detection for MTC patients in China, and bring out some managements for individuals after detection of RET mutations that are high risk for MTC.

Minor comments:

Title and abstract:

"A rare C620Y variant in RET in Chinese family" is not good, because it may contain alternative meaning. First: C620Y mutation is rare in familial MTC. Second: C620Y mutation is rare in China. In addition, "A rare C620Y variant in RET in Chinese family" means C620Y mutation is rare among the various mutations in RET oncogenes in Chinese. In China, do physicians examine the RET oncogene mutation in daily clinical work? What is the dominant mutation in the sporadic MTC?

RE: Thanks for your suggestions, wo had revised the title of our manuscript. The new title was “Chinese siblings with hereditary medullary thyroid carcinoma caused by RET mutation: implications for RET oncogene detection”.

At present, there are no guidelines for the diagnosis and treatment of MTC in China, and clinical practice is mostly implemented in accordance with the relevant guidelines of the American Thyroid Association (ATA). Despite this, the diagnosis and management of MTC are not uniform among the centers in China. In the MTC guidelines published by ATA, the detection of RET oncogene mutation closely associated with MTC is recommended, and has become the daily clinical work. In China, however, many patients even clinicians pay less attention on RET oncogene detection. In addition, the genetic detection is expensive and is not yet covered by Medicare, therefore, the examination of the RET oncogene mutation for MTC patients is not the daily work of Chinese physicians.
(Endoscopic) ultrasonography could detect MTC, however, could not confirmed.

RE: Indeed, ultrasonography could not confirm the diagnosis of MTC. For patient 2, the confirmation of MTC was the postoperative pathological examination. We had revised the corresponding description in the abstract.

If authors use MTC for abbreviations, unify throughout the abstract.

RE: Thanks for your kind suggestion, we had used MTC for abbreviations throughout the abstract.

Background:

Because authors emphasize the importance of p.C620Y mutations in RET, description about pC620Y mutation helps readers to understand the importance of this report.

RE: We had revised our manuscript which weaken the importance of p.C620Y mutations in RET.

In addition, is MTC frequency in China different from other countries?

RE: There is significant difference in the hereditary MTC frequency between China and foreign countries. According to foreign reports, the hereditary MTC accounts for about 20%-30% of all MTC. However, in China, the MTC frequency were less than 3% according to a study conducted in clinical center of Shengjing Hospital affiliated to China Medical University. (Qiyuan Gao et al. Analysis of postoperative survival and prognostic factors for patients with medullary thyroid carcinoma. Chinese journal of general surgery. 2018,27(11),1377-1386). It is of great possibility that the hereditary MTC frequency in China is underestimated because of the inattention by patients and clinicians, and the high price of genetic detection.

Case presentation:

Patient 1

How about the calcitonin and CEA levels? After the total thyroidectomy with lymph node dissections, these levels decreased to reference levels? In addition, patient is planned for further chemotherapy for residual FMTC?

RE: The pre- and post-operative calcitonin and CEA levels had been added in the Table 1. And corresponding description was also supplemented in the case presentation sections. The postoperative calcitonin and CEA levels were still higher than the max reference value, but decreased significantly compared with that before surgery. Since the insensitivity of FMTC to
chemotherapy and radiotherapy, as well as the unavailability of Vandetanib in China, the patient only received hormone replacement treatment by supplementing with thyroid hormone.

How about the hyperparathyroidism or pheochromocytoma as MEN type 2?

RE: Both patients were investigated for the endocrinological features of MEN2A and MEN2B; on examination and investigation, none could be found.

How about the hypoparathyroidism after the total thyroidectomy? Is the parathyroid gland could be preserved?

RE: the parathyroid gland was preserved during the surgery, and no hypoparathyroidism after the total thyroidectomy was found. We had added this information in the case presentation section of patient 1.

Patient 2

"….. vitamin D3 tablets (II) at a dose of 50 g … (Line 50 , page 3)" What is "II"?

RE: Vitamin D3 tablets (II) is the drug names on the product packaging. We are sorry for the lack of standardization in drug names. We had revised this mistake in our manuscript.

Follow-up and outcomes

Describe the details about missense mutations of p.C620Y. Substitution of base.

RE: Thanks for your suggestion, we had added the details of RET p.C620Y mutation. The description was as follow: “The RET p.C620Y variant is caused by a cysteine to tyrosine amino acid change, and is considered to result in ligand-independent receptor dimerization and cross-phosphorylation”.

Why do the authors evaluate the patients as satisfactory therapeutic results? How about the metastasis? Did authors explore? Detailed description is required, because they discuss the importance of p.C620Y mutation on prognosis of the patients in followed discussion section.

RE: Both patients had received follow-up after 10 months after surgery. No obvious tumor metastasis was found, and the CEA and calcitonin level also did no increase obviously. Therefore, we evaluate the patients as satisfactory therapeutic results. Considering that this paragraph is meant to descritp the result of genetic detection for the patients and their family members. We had removed the first sentence and revised the section titles as “Genetic
detection”. For the discussion section, we also revised thoroughly, and details please read the revised manuscript.

Discussion and conclusions:

"Currently, more than 100 RET ….. extracellular cysteine-rich domain [4]. (Lines 67 to 69, page 3)" and "This variant is ….. no more than 1% [5, 6] (Lines 71 to 72, page 4)"

Authors described codon 620 is common mutation; however, p.C620Y mutation is no more than 1%. Other mutations in codon 620 have specific phenotypes? Authors discussed clinical features of p.C620Y and their cases, however comparisons with other common mutations in p.620 may help readers' understandings.

RE: These sentences were aimed to describe the low incidence rate of RET p.C620Y variant. There are no specific phenotypes in MTC patients with other mutations in codon 620. To perfect our manuscript, we had deleted the sentence of “whereas, its occurrence rate is no more than 1%”. In addition, we had revised our manuscript thoroughly, especially the discussion part. The details please read the revised manuscript.

"Our report also …. counseling in MTC. (Lines 90 to 91, page 4)."

Authors do not describe the importance of counseling in manuscript. If the authors conclude that issue, denote that issue in the manuscript.

RE: Thanks for your suggestion. We had revised this sentence in the corresponding part.

Tables and Graphics

Figure 1(E): Single parent can produce child?

RE: We are sorry for the wrong figure and corrected this mistake.