Dear Professor Jin-Zhou Tang,

Thank you very much for your letter. We would also like to thank all reviewers. They gave us encouraging and constructive comments. Our manuscript was further improved by incorporating and implementing the comments of the reviewers before re-submission. We tried our best to make a clearer focus and incorporation of referees' suggestions.

Title: Growth hormone therapy for children with KBG syndrome: a case report and literature review. No:52469.

With regard to the reviewers' comments and suggestions, we wish to reply as follows:

To reviewer 1:

Dear professor,

We really appreciate your precious and constructive suggestions. Thank you very much. All changes were in red color in the manuscript so that they may be identified. The numbers of line are according to words.

1. In the Abstract, Case Summary should include data from the authors' patient. Cases reported in the literature can be grouped under Reported Cases.
Reply: Data from our patient was included in the summary "GH treatment is effective in our girl and most KBG children with short stature during the first year of therapy". (On page 2 line 23-24)
"In previous studies" was corrected into "in reported cases". (On page 2 line 19)

2. In the Abstract, under Conclusion, the authors can only conclude that growth hormone therapy is effective in most children with KBG syndrome for the first year of treatment. Further study on the effectiveness of long-term use and improvement in adult heights is needed.
Reply: The conclusion was corrected "GH treatment is effective in our girl and most children with KBG syndrome accompanied by short stature during the first year of therapy." (On page 2 line 23-24)

3. Do not use the term "KBG children". Use children affected by KBG syndrome please.
Reply: In this article, there were often descriptions after "children with KBG syndrome". We used lots of "KBG children" to avoid using too much "with".
"KBG children" has been described in some literatures: "Reynaert, N., Ockeloen, C. W., Sävendahl, L., et al. (2015). Short stature in KBG syndrome: first responses to growth hormone treatment. Hormone research in paediatrics, 83(5), 361-364"."Brancati, F., Sarkozy, A., & Dallapiccola, B. (2006). KBG

syndrome. Orphanet journal of rare diseases, 1(1), 50". "Hah, M., Lotspeich, L. J., Phillips, J. M., Torres, A. D., Cleveland, S. C., & Hallmayer, J. F. (2009). Twins with KBG syndrome and autism. Journal of autism and developmental disorders, 39(12), 1744-1746."
"KBG children" has been revised in this article according to your suggestions.

4. The Core Tip is not clear. Give a clear message what the authors would like to reader to bring home.
Reply: Core Tip was corrected. "KBG syndrome is a rare autosomal dominant disorder. The percentage of height below 10th centile was 66%. It is relatively high. Children with KBG syndrome accompanied by short stature could benefit from growth hormone therapy". (On page 3 line 1-3)

5. Under Introduction, there is no need to discuss the diagnostic criteria for the KBG syndrome. Omit the second paragraph.
Reply: Thank you very much for your comments. Please give me an opportunity to explain the reasons for quoting the diagnostic criteria: firstly, in order to provide evidence for the diagnosis of KBG syndrome in our cases; secondly, in order to show the percentage of short-stature in KBG syndrome.

6. There is no need to introduce an abbreviation to multi-disciplinary team.
Reply: The abbreviation of multi-disciplinary team was deleted. (On page 4 line 23)

7. Under Introduction, the authors should remove the data about their own case in this section. It is a duplication of data in the report.
Reply: Data about our case in introduction was deleted.

8. Under Case Presentation, please combine history of present illness and history of past health into one single section. Past health refers to those parts of the history that are not relevant to the presenting problem. Developmental delay is an integral feature of the KBG syndrome and should therefore be included under present illness. Delete the current height in the history. This is again a duplication of what the authors were telling later.
Reply: According to the format requirements of this journal, there should be two parts of "history of present illness" and "history of past illness".
The part of developmental delay was written in the part of "history of present illness".
The part in "history of past illness" was corrected into "Past medical history was unremarkable except for developmental delay."
The current height in the history was deleted. "Her height was below the mean for age (less than the 3rd percentile) ". (On page 5 line 10-18)

9. It is quite unusual to diagnose developmental delay at 2 months old. What was actually delayed in development?
Reply: Developmental delay at 2 months old was diagnosed in her local community

hospital. I'm sorry that the specific description is unknown.

10. Family history should stand alone. The child birth history has already been mentioned earlier and there is no need to repeat it again.
Reply: According to the format requirements of this journal, there should be one part of "personal and family history". I've removed the repeated part in personal history. "No specific personal history of disease was recorded." (On page 5 line 18)

11. Change Laboratory Examinations to Laboratory Investigations.
Reply: "Laboratory examinations" is required according to the format of this journal. I am so sorry.

12. Under Laboratory Investigations, give the normal reference ranges for the peak growth hormone after stimulation tests. Also provide the method used for the assay of growth hormone in the authors' laboratory.
Reply: The normal reference ranges for the peak growth hormone and the method used for the assay of growth hormone in laboratory were added. "The cut-off peak GH value for growth hormone deficiency was ≤10 ng/ml". "Serum GH level was measured using chemiluminescence assay (Cobas E170, Roche Diagnostics, Germany)". "Serum IGF-1 were measured using chemiluminescence assay (Siemens Healthcare Diagnostics, USA)." (On page 6 line 2-6)

13. Was growth hormone deficiency confirmed, excluded, or not certain? "Considered" is not an appropriate word in this sentence.
Reply: The sentence was corrected into "The cut-off peak GH value for growth hormone deficiency was ≤10 ng/ml. Growth hormone deficiency was confirmed". (On page 6 line 3)

14. There is no need to mention the genetic workup for the case. This is not the focus of the report. The authors can just mentioned the heterozygosity for the genetic mutation found during the investigation of the index patient.
Reply: Thank you very much for your comments. Please give me an opportunity to explain the reasons to mention the genetic workup for our case: firstly, make a definite diagnosis of our patient with KBG syndrome which is determined by gene tests; secondly, in order to prove there was a new and significant mutation in our patient according to the guidelines of ACMG"

15. Change Imaging Examinations to Imaging.
Reply: "Imaging examinations" is required according to the format of this journal. I am so sorry.

16. Under Imaging, provide the reference/method how the patient's bone age was reckoned.
Reply: Bone age is estimated using the atlas of Greulinch-pyle. (On page 6 line 11)

17. Why was the patient's intelligent quotient listed under Imaging?
Reply: Intelligence testing was added as a new part. (On page 6 line 14). Thank you very much for your suggestions.

18. Delete the section Final Diagnosis.
Reply: "Final Diagnosis" is required according to the format of this journal. I am so sorry.

19. Under Outcome and Follow-up, did the patient receive 2 years of treatment with growth hormone and then the treatment was discontinued? If the patient was still on growth hormone after 2 year, the authors should state "Follow-up was performed every three months for two years."
Reply: The patient is still on growth hormone therapy. We corrected according to your suggestions. "Follow-up was performed every three months for two years." (On page 6 line 25). Thank you for your suggestions.

20. Under Discussion, the authors should state clearly in the first paragraph what they wanted to study and compare when they collected cases published in the literature. The comparison of the growth changes at after 1 year of growth hormone treatment was the main focus. Similarly, they should also state clearly and logically that cases were excluded if the growth data and follow-up information were incomplete. In this manner, those cases with follow-up less than one year should be excluded. Also, those patients whose duration of follow-up was not clear should also be excluded. Therefore, five patients mentioned for comparison should be excluded. And the subsequent discussion should be modified to accommodate for such changes.
Reply: Thank you very much for your comments. The first paragraph of discussion was corrected "In this study, we collected data of children with KBG syndrome accompanied by short stature. To observe the effects of GH therapy on the height of children with KBG syndrome accompanied by short stature, we mainly analyzed growth velocity during the first year comparing those with and those without GH therapy. (On page 7 line 2-5)
KBG syndrome is a rare disease. Cases with height changes before and after GH therapy is very rare. The data is even less If we delete some cases. Therefore, we keep data as much as possible. We corrected the discussion to state clearly and logically. (On page 7 line 2-17)

21. The growth velocity of the index patient during the second year of growth hormone treatment was obviously slower than that of the first year. Is there a possibility that growth hormone treatment may lose its effectiveness on longer term treatment?
Reply: Growth rate in the first year can predict the long-term therapeutic effect of GH. Reference is as follows: Kriström, B., Dahlgren, J., Niklasson, A., Nierop, A. F., & Albertsson-Wikland, K. (2009). The first-year growth response to growth hormone treatment predicts the long-term prepubertal growth response in children. BMC

medical informatics and decision making, 9(1), 1.
However, it has not been reported for KBG syndrome. Further research is needed.

22. About the limitations of the study, the authors should mention that the effects of growth hormone on children with the KBG syndrome in longer term are not known. There is no data on its beneficial effect in the final adult height.
Reply: The limitations was added. “The long-term effects of GH therapy on children with KBG syndrome and its benefits to adult height are not clear.” (On page 8 line 16-17)

23. In the Conclusion, the authors can only state that there is a good response to growth hormone for the first year of treatment. The statement that growth hormone is effective in most children with the KBG syndrome with short stature is imprecise and not supported by the Discussion. Similarly, the Discussion does not provide sufficient evidence for growth hormone treatment under such conditions.
Reply: This was corrected in conclusion. “In conclusion, our girl with KBG syndrome showed a good growth response to the first year of GH therapy. We reviewed and analyzed the changes in the height of children with KBG syndrome accompanied by short stature during the first year of therapy in the reported cases. We conclude that GH treatment is effective in our girl and most children with KBG syndrome accompanied by short stature during the first year of therapy. Our results provide evidence for GH treatment in children with KBG syndrome accompanied by short stature”. (On page 8 line 21-26)

24. Table 1 has alignment problems.
Reply: There are many rows in the table due to the large amount of data. It is not easy to align the table. I am so sorry.

25. Figure 1 is not needed. It is not related to the growth data or growth hormone treatment.
Reply: Thank you very much for your comments. Figure 1 can show there was a new and significant mutation in our patient. In this paper, we aimed to report a new case with KBG syndrome and review literatures of growth data or growth hormone treatment for children with KBG syndrome.

26. In Figure 3, the 2 cases with follow-up less than 1 year and the 3 cases with unknown follow-up period should be deleted. They only serve to confuse the readers.
Reply: Thank you very much for your comments. Cases with height changes before and after GH therapy is very rare. The data is even less If we delete some cases.
The authors of 3 cases with unknown follow-up period proposed in their articles that “catch up height (P4).” “This treatment was successful(P9)””Height <3rd and improved to 25th with growth hormone(P10)”

To reviewer 2:

Dear professor,

We really appreciate your precious comments and correction extremely. Thank you very much. All changes were in red color in the manuscript so that they may be identified. The numbers of line are according to words.

I reviewed with interest this case report. I have the following comments The authors used to say KGB girl, KGB children. They should say a girl with KBG syndrome or children with KGB. Always give the humanity a priority over the disease. Plz correct that in all the manuscript. In the Cor Tip The first line: the author said Incidence; it is not incidence, it is a percentage Introduction First paragraph: Plz correct that in all the manuscript. Third paragraph: [What about the effects of growth hormone (GH) therapy on KBG children with short stature?]. This is an Interrupting sentence; needs to be removed or changed Case Presentation In Chief complaints': The author wrote the age as 5.5 y. It should be written as 5 ys & 5 months or 5 5/12 Yrs. Please not that in all the manuscript History: should be one item rather than dividing it into three to avoid repetition and wrong placement of data In Physical examination: It will be better illustration if there is a photo for the patient if they got permission to do that TREATMENT: The dose of growth hormone 50 μg/kg/d, Was this the starting and maintenance dose through the 2 yrs of treatment?? Can the authors summarize clear indication of growth hormone therapy, the proposed dose and follow up parameters of growth hormone therapy in children with KGB syndrome?

Reply:
"KBG children" has been revised in this article according to your suggestions.
"The incidence" was corrected into "The percentage" (On page 3 line 1)
"What about the effects of growth hormone (GH) therapy on KBG children with short stature?" was corrected into "The effects of growth hormone (GH) therapy on children with KBG syndrome accompanied by short stature are not clear." (On page 4 line 24-25)
"The 5.5 years" was corrected into "A Chinese girl aged 5 years and 6 months"
According to the format requirements of this journal, there should be three parts of history. I've removed the repeated content in "History of present illness, History of past illness,Personal and family history"(On page 5 line 7-18)
The parents of the patient don't agree to show her photos. I am so sorry.
The maintenance dose is basically about 0.15iu/kg/d (50 μg/kg/d). The main changes in total dose of GH depend on body weight. There are only three cases reported the GH dose in the literature.The evidence of recommended dose is insufficient. Our follow-up time is short. The proposed dose and follow up parameters of growth hormone therapy in children with KGB syndrome still need large-scale and long-term multicenter study to recommend.