Dear Dr Eleni Papageorgiou:

Thank you for your letter and for the reviewers’ comments concerning our manuscript entitled ‘Luxation of bulbus oculi in Crouzon syndrome: a case report’. (ID: BOPH-D-19-00517). Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied comments carefully and have made correction which we hope meet with approval. Revised portion are marked in red in the paper. The main corrections in the paper and the responds to the reviewer’s comments areas flowing:

Responds to the reviewer’s comments:

Response to Reviewer 1: Dr F Hariri

1. Response to comment: The title indicating clinical report, but the manuscript has more genetic content.
Response: Thanks for your suggestion. We have made correction according to the Reviewer’s comments. We change our title to ‘Inherited FGFR2 mutation in a Chinese patient with Crouzon syndrome and luxation of bulbus oculi provoked by trauma: A case report’.

2. Response to comment: It requires minor grammatical correction or information rephrasing. Example; in abstract (introduction and conclusion) and main manuscript (introduction and discussion); It contains 2 sentences, which are contradicting to each other;

* Page 2 line 30 and Page 3 line 20: Crouzon syndrome (CS) is one of the causes of fibroblast growth factor receptor 2 mutations.

* Page 3 line 1 and Page 5 line 29: Crouzon syndrome is caused by FGFR2 mutations.

Response: We are very sorry for our incorrect writing. In abstract ‘introduction and conclusion’ have re-written to ‘introduction and discussion’. Page 2 line 30 the statements of "Crouzon syndrome (CS) is one of the causes of fibroblast growth factor receptor 2 mutations” were corrected as "Crouzon syndrome (CS), which results from fibroblast growth factor receptor 2 mutations”. Page 3 line 20: the statements of "Crouzon syndrome (CS) is one of the causes of fibroblast growth factor receptor 2 mutations." were corrected as "Crouzon syndrome (CS), caused by fibroblast growth factor receptor 2 (FGFR2) mutations, is associated with craniosynostosis".

3. Response to comment: The term 'a surprised look' (Page 4 line 24) can be described as 'proptosed' or at least written with quotation mark (‘…’)

Response: We are very sorry for our negligence of our presentation, Page 4 line 24 we have described their ’a surprised look’ with quotation mark in red in revised paper.

4. Response to comment: Please state the mannitol, tobramycin eye ointment and carbomer eye drops full prescription protocol.

Response: Thanks for your advice. As Reviewer suggested that we have detailedly stated the full prescription protocol of every drug in red in revised paper. ‘Therefore, mannitol (10 g, q8h, intravenous drip) was administered for symptomatic reduction of orbital pressure for three days. At the same time, tobramycin eye ointment (topical instillation, qn) and carbomer eye drops (topical instillation, q8h) were administered to the left eye for 3 days to protect it from exposure keratitis and obstinate conjunctivitis’ in Case presentation part paragraph 2.

5. Response to comment: The author should mention treatment duration and follow up period for the patient.

Response: Thanks for your advice. It is really true as Reviewer suggested, we have described ‘The treatment duration was for 3 days’ and ‘The patient was re-examined at our hospital one week after discharge. There was no obvious dislocation of the eyeball. The BCVA of left eye was maintained at 0.2. Subsequently, the patient was lost to follow-up’ in Case presentation part paragraph 2.
6. Response to comment: The discussion section contains clinical and genetic aspects of Crouzon syndrome. What does the author mean by stating 'our results indicate a rare symptom in this disease' (Page 6 line 15)? This should be well elaborated.

Response: Thanks for your advice. We have deleted Page 6 line 15 ‘Our results indicate a rare symptom in this disease’ and re-written this part to ‘The clinical characteristics of our patient supported a diagnosis of CS, while there are a few reports of luxation of the bulbus oculi in Chinese families with CS. It is of interest that our patient had ocular proptosis and shallow orbits, combined with luxation of the eyeball after trauma.’ according to the Reviewer’s suggestion in revised paper.

Special thanks to you for your good comments.

Response to Reviewer 2: Dr N Al-Namnam

1. Response to comment: Can authors please explain how the results of this study “enhance the current knowledge of CS phenotypic and genotypic heterogeneity, but also assist genetic diagnoses of a rare symptom in patient”? How the genetic retesting affected the particular symptom in the presented case?

Response: Thank you for your advice. We have rephrased this statement as the luxation was provoked by the trauma due to the shallow orbits present in patient with Crouzon syndrome. We have re-written this part according to the Reviewer’s suggestion. This part is described as ‘Edema of the periorbital tissue is observed in the event of blunt injuries to the forehead and periorbital area. The shallow orbits observed in patients with CS patients have limited space to accommodate edematous tissue. Therefore, these patients are more likely to develop eyeball luxation. Our findings enhance the current knowledge of CS concomitant with traumatic luxation of the eyeball’ in revised paper.

2. Response to comment: Crouzon syndrome (CS) is one of the causes of fibroblast growth factor receptor 2 mutations related to craniosynostosis, It should be” results from" not "causes of".

Response: We are very sorry for our incorrect writing, and we have made correction according to the Reviewer’s comments. The statements of " causes of " were corrected as " results from " in page 1 paragraph 1.

Special thanks to you for your good comments.

Response to Reviewer 3: Anastasia Pilat

1. Response to comment: Authors state that they " have attempted to report a rare symptom in CS”. In the described circumstances this is not a symptom of the Crouzon syndrome, otherwise it would be present without triggering trauma. Authors need to rephrase this
statement as theluxation was provoked by the trauma due to the shallow orbits present in patient with Crouzon syndrome.

Response: Thank you for your kind advice. We have re-written every part according to the Reviewer’s suggestion in revised paper. We have rephrased our statement ‘have attempted to report a rare symptom in CS’ to ‘Herein, we report the genetic abnormalities detected in a Chinese family with autosomal dominant CS, combined with luxation of the eyeball. This luxation was a consequence of the trauma to the shallow orbits’ in page 1 paragraph 1 and ‘We report the genetic abnormalities in a Chinese family with autosomal dominant CS combined with luxation of the eyeball in this study. It is noteworthy that the luxation in our patient was a sequela of trauma to the shallow orbits’ in Background part paragraph 1.

2. Response to comment: In the case presentation section I would suggest authors to describe all findings related to the proband and particular trauma case: findings just after the trauma, what treatment has been done, ocular findings after treatment (including eye movements, presence of strabismus/diplopia; nerve function-RAPD, nerve appearance, intraocular pressure).

Response: Thank you for your well-meaning advice. We have presented all findings related to the particular trauma case pretherapy and posttreatment. ‘The eye movements were restricted in all directions. External strabismus was also observed. The relative afferent pupillary defect (RAPD) was negative’ in Case presentation part paragraph 2. ‘The restriction in eye movement improved after treatment. However, mild restricted internal eye movement and mild external strabismus were observed’ in Case presentation part paragraph 2. We have described treatment: ‘Therefore, mannitol (10 g, q8h, intravenous drip) was administered for symptomatic reduction of orbital pressure for 3 days. At the same time, tobramycin eye ointment (topical instillation, qn) and carbomer eye drops (topical instillation, q8h) were administered to the left eye for 3 days to protect it from exposure keratitis and obstinate conjunctivitis’ in Case presentation part paragraph 2.

But we are very sorry for description of nerve appearance and intraocular pressure, because the child was unable to cooperate with intraocular pressure and fundus examinations.

3. Response to comment: Can authors please clarify what was actual visual acuity at the time of presentation? "The visual acuity of his left was at stake …" 

Response: Thank you for your advice. We have clarified ‘The best corrected visual acuity (BCVA) of individual III:2 (4 years old) was 0.5 for the right eye, and 0.1 for the luxated left eye’. ‘The visual acuity of the left eye was in a precarious condition due to severe exposure keratitis and traumatic dislocation of the eyeball’ in Case presentation part paragraph 2, we have revised them in revised paper.

4. Response to comment: Can the intraocular pressure be clarified as well?

Response: Thank you for your advice. We agree with your advice and we think intraocular pressure is very important for this particular trauma case, but the child was unable to cooperate with intraocular pressure examinations, so we can’t get data successfully.
5. Response to comment: Figures need to be re-written. What is the difference in the results between CT and MRI? Authors need to comment what they want us to see on the scans? If it is ocular proptosis of the proband why on CT the sizes of the eyeballs look different? Is it motion artefact? Authors state that the facial photographs of the affected subjects are shown. Only eye/orbital appearance is seen. These are not facial photos.

Response: We have made correction according to the Reviewer’s comments. We have revised ‘Computed tomography and magnetic resonance imaging did not reveal retrobulbar hematoma and revealed shallow orbits and ocular proptosis in patient III:2’ in Case presentation part paragraph 2 and Figure 2 legend. We are very sorry for our negligence of CT the sizes of the eyeballs. The figure have been re-written, CT scan photo was deleted and replaced to another photo that eyeballs sizes looked accordant. We are very sorry for we can’t show the facial photos, because identifying/confidential patient data should not be shared in accordance with BioMed Central editorial policies and formatting guidelines.


Response: We are very sorry for our negligence of referring to other publications. We have quoted from other publications in revised paper.

7. Response to comment: Can authors please explain how the results of this study "enhance the current knowledge of CS phenotypic and genotypic heterogeneity, but also assist genetic diagnoses of a rare symptom in patient"? How the genetic retesting affected the particular symptom in the presented case?

Response: Thank you for your advice. We have re-written this part according to the Reviewer’s suggestion. This part is described as ‘In conclusion, we identified a mutation in FGFR2 that caused CS. Edema of the periorbital tissue is observed in the event of blunt injuries to the forehead and periorbital area. The shallow orbits observed in patients with CS patients have limited space to accommodate edematous tissue. Therefore, these patients are more likely to develop eyeball luxation. Our findings enhance the current knowledge of CS concomitant with traumatic luxation of the eyeball’ in revised paper.

8. Extensive revision of English is needed before the publication will be accepted.

Response: Thank you for your advice. We have reviewed our manuscript by someone who is fluent in English and hope that the correction will meet with approval.

Special thanks to you for your good comments.
We tried our best to improve the manuscript and made some changes in the manuscript. These changes will not influence the content and framework of the paper. And here we listed most of changes and marked in red in revised paper.

We appreciate for Editors/Reviewers’ warm work earnestly, and hope that the correction will meet with approval.

Once again, thank you very much for your comments and suggestions.

Yours sincerely,

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