Author's response to reviews

Title: Reduced transcription of TCOF1 in adult cells of Treacher Collins syndrome patients

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Author's response to reviews: see over
Dear Dr. Helen Whitaker,

We are enclosing the manuscript “Reduced transcription of TCOF1 in adult cells of Treacher Collins syndrome patients” after including the reviewers’ suggestions, as detailed below. We also considered your suggestion and asked a native English speaking colleague to read the final version of this paper. We would like to take this opportunity to thank for the comments and we are confident that this new version will be accepted for publication in BMC Medical Genetics.

We are looking forward to hearing from you.

Sincerely yours,

Prof. Dr. Maria Rita Passos Bueno

Cibele Masotti, PhD.

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Answer to the reviewer Dr. Paul Trainor:

1) **Major compulsory revision:** “The major issue arising from this paper however is the lack of any relevance for TCOF1 haploinsufficiency during adult life. The authors note, the prognosis for mandibular distraction in TCS patients is often poor and hypothesize this could be connected to a stem cell deficit. However there is no evidence to back up these claims and thus no significance can be attributed to adult haploinsufficiency. The authors should take their patient specific mesenchymal cell populations and differentiate them into cartilage and bone in culture and assess the capacity of these cells to proliferate, survive, apoptose as well as their efficiency to form chondroblasts, chondrocytes, osteoblasts, osteoclasts etc. If adult haploinsufficiency is relevant there should be noticeable differences between TCS mesenchyme versus control mesenchyme.”

Authors’ answer: Based on these comments, we have reformulated the second paragraph of page 5 (Background) and the last paragraph of page 13...
(Conclusions). We also included another reference suggesting the importance of treacle in adulthood (Goverdhan et al., 2005).

We think that the relevance of TCOF1 haploinsufficiency in adult cells has not been well studied, and our findings, particularly in mesenchymal cells, open new possibilities to test this hypothesis. In agreement with the reviewer’s suggestion, as soon as we establish enough number of stem cell cultures of patients with Treacher Collins syndrome, we are planning to test the effect of TCOF1 levels in osteogenesis and chondrogenesis in vitro.

2) **Minor essential revision:** “The reference to the Dixon et al. (2006) paper is incorrect when it quotes a high incidence of cell death in neural crest cells. The apoptosis is occurring in the neuroepithelium and not in the neural crest. My understanding is that with respect to the neural crest these cells only displayed reduced proliferation compared to wild type neural crest cells.”

**Authors’ answer:** In agreement with the reviewer’s comment, we have rephrased this citation in the first paragraph of page 5.