Reviewer's report

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

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Reviewer: Paul Trainor

Reviewer's report:

The authors have revised the paper accordingly.

The novel contributions of the paper are firstly that it identifies and documents 8 new mutations in the TCOF1 that contribute to the manifestation of Treacher Collins syndrome. Secondly the authors confirm nonsense mediated decay as part of the underlying genetic mechanism. Although this has previously been suggested from the types of mutations found in TCOF1, it had never fully been demonstrated in patients with TCS. Interestingly, only 2 of the 4 patients had an undetectable mutant allele. Of the patients with a detectable mutant allele, TCS18 possesses an inframe deletion which may disrupt the nucleolar localisation of Treacle. One could argue this suggests that Treacle mislocalisation could be just as important as haploinsufficiency in the pathogenesis of Treacher Collins syndrome. Thirdly partial wild-type allele compensation may occur but will differential efficiency in different tissues. For example only an 18% reduction was observed in leucocytes while in mesenchymal cells it was 31%.

To date it is not know if there are any consequences for TCOF1 nonsense mediated decay and Treacle deficiency in adults, however, the authors speculate this may explain why the surgical repair prognosis for Treacher Collins patients undergoing mandibular distraction procedures for example are typically not as good for patients with other syndromes. This seems like a reasonable hypothesis and it would have been ideal for the authors to test and compare the bone forming efficiency of mesenchymal cells derived from their control and Treacher Collins patients. Nonetheless this will be an important issue to address in the future.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests