Reviewer’s report

Title: Genetic Heterogeneity of Ellis-van Creveld in the United Arab Emirates

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Reviewer: Zhuan Bian

Reviewer’s report:

The authors reported six EvC cases from four UAE families. Candidate gene sequencing revealed a novel splice site mutation and two recurrent mutations. I think the manuscript needs major compulsory revisions and I’m unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions.

Detailed comments:

1. The author should be cautious to use the phrase “genetic heterogeneity” in the title of this manuscript. Direct sequencing can not detect some kind of mutation, such as gross deletion or duplications. In addition, the author didn’t sequence the UTR regions of the disease cause genes. It is still possible that in the fourth family, there lies EVC or EVC2 mutations which could not detected by sequencing technique or have not been detected yet. Also, the author didn’t provide evidence for exclusive linkage of this family to EVC or EVC2. So there’s not enough evidence to consider genetic heterogeneity in this case. I suggest the author to modify the title. The abstract part has the same problem.

2. Key words are not very good and should be modified.

3. In the abstract section, “...a novel splice site mutation (IVS13-1G>T) in exon 14...”. This mutation lies in intron 13 but not exon 14.

4. In the first paragraph of introduction, the descriptions of disease prevalence should be uniform, i.e. all of them should be “per 1,000,000”, or “per 10,000”.

5. Of the second paragraph in introduction section, the first line should be indented.

6. In the first paragraph of materials and methods section, the author should list the detailed diagnosis criteria. If these criteria were from other publications, the references should be listed. Another disorder, Weyers acrofacial dysostosis, has most similar clinical manifestations to EvC; it is also allelic to EvC. The author should point out why the six cases were diagnosed as EvC but not Weyers acrofacial dysostosis.

7. In the results section, the description of patients’ phenotypes is verbose. A table contains different clinical features category of these six cases would be clear and much easier to understand.

8. In the results section, the author should sequence the candidate genes of patients’ parents to trace the origin of these mutations. Only when the parents carry the same heterozygous mutation can the author definitely describe the
disease as “recessive model”.

9. As for the novel splice mutation, it seemed that the author didn’t carry out a population based mutation screening in normal health controls.

10. The title for table 2 should be changed. The word “haplotype” was misused here because this table has nothing to do with any kind of haplotype. Listed known SNPs would not provide more useful information to this manuscript. If SNPs detected in family 1 and 4 were shown, why the author didn’t list the SNPs detected in the other two families? What’s more, table 3 could be merged into table 2.

11. The figures should contain the pedigree structures of the four families. And for the two recurrent mutations, the sequence chromatograms should also be included.

12. In several places, gene symbol should be italic, such as EVC or EVC2. The English writing was not very good and needs improvement.