Author's response to reviews

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

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Author's response to reviews:

Dear Editor,

We thank you for allowing us more time to respond to the extensive reviewers’ comments. We greatly appreciate their efforts and thank them for allowing us to improve the manuscript. We accepted most of their comments and we have addressed them as the following:

Reviewer 1

Point 1: We agree with the reviewer comment and we, therefore, have changed the title of the article to “Molecular and clinical analysis of Ellis-van Creveld syndrome in the United Arab Emirates”

Point 2: We modified some of the keywords as suggested by the reviewer

Point 3. The name of the novel mutation has been changed to c.1806-1G>T (IVS13-1G>T) and we corrected the location to intron 13 as correctly pointed out by the referee.

Point 4. Disease prevalence unified to per 100,000.

Point 5. Paragraph now indented

Point 6. Diagnosis criteria included in the section now and differential diagnosis from related condition is presented in the discussion section

Point 7. A table (table 2) is included to summarize the phenotypes of the patients.

Point 8. We did sequence the parents (if DNA is available) and in those cases we found them heterozygous to the reported mutations.

Point 9. This splice site mutation has not been found in 100 ethnically matched controls (this now added to the results)

Point 10. The title of the mentioned table has been changed. We also removed the SNPS found in the index case of family 4 as we agree it doesn’t add useful information to the manuscript.
Point 11. We added figure 1 that shows the pedigrees of the 4 families; we also included the chromatograms of the other recurrent mutations (Figure 3).

Point 12. The gene symbols are italicized throughout the manuscript and the English has been improved.

Reviewer 2

Point 1 (The title). Title has been changed to “Molecular and clinical analysis of Ellis-van Creveld syndrome in the United Arab Emirates”

Point 2 (Abstract). We accept and the abstract has been changed to reflect this point.

Point 3 (Discussion). Discussion has been modified and including clinical features and differential diagnosis from related conditions.

Point 4. We are unable to provide pictures of patients. The clinical data of the cases reported here are typical for the conditions.

Point 5 (Discussion). We are discussing the family 4 phenotype in relation to Jeune syndrome

Point 6 (writing). The English Language has been improved.

Reviewer 3

Point 1. Title changed as suggested by the first 2 reviewers.

Point 2. Polydactyly is now included in the keywords

Point 3. Point accepted and we are using the short name EvC throughout the manuscript.

Point 4. Uluncan has been changed to Ulucan

Point 5. Phrase deleted

Point 6. Uluncan has been changed to Ulucan

Point 7. neonatologists is kept because the patients were seen by several neonatologists.

Point 8. Percentiles have been added as requested

Point 9. Ethnicities is now included for each family in the text and table 2.

10. ?? Lihadh

11. Phrase has been changed as suggested

Point 12. Phrase has been changed as suggested

Point 13. Changed as requested

Point 14. Text modified for more clarity on this point

Point 15. Changed as suggested (murmer to murmur)

Point 16. EVC and EVC2 gene name have been italicized as suggested

Point 17. Text has been changed as suggested

18. EVC and EVC2 are italicized throughout the manuscript
19. Point taken and manuscript modified accordingly

Point 20. Tables 2 has been modified and changed to table 3 and old table 3 is now table 4. The text has been changed as well.

Reviewer 4

Point 1 (first sentence). Introduction modified to reflect the suggested changes.

Point 2 (Materials and Methods). The text has been modified accordingly.

Point 3 (Results). We don’t think it is relevant to include date of and place of birth of the patients.

Point 4 (Results). The phenotype in family 4 fits with EvC and is discussed in relation to other overlapping phenotypes. Lack of mutations in EVC and EVC2 have been reported in two thirds of patients with EvC and therefore confirming the possibility of involvement of other unidentified gene(s). In the light of this, we would like to keep this family in the study.

We believe that we have addressed the comments adequately and therefore we hope that the manuscript is now acceptable for publication in BMC Medical genetics.

Looking forward to hearing from you positively

Best Regards,

Bassam Ali