Reviewer's report

Title: Isolated brachydactyly type E can be caused by HOXD13 nonsense mutation: case report

Version: 2 Date: 24 November 2011

Reviewer: Georg Schwabe

Reviewer's report:

The manuscript „Isolated Brachydactyly Type E Caused by a HOXD13 nonsense mutation: a case report“ by Jamsheer et al. has improved significantly by the additional changes performed. However I recommed further minor essential revisions before publication.

1. The delineation of the HoxD13 genotype-phenotype introduced by the authors in Table 2 and Figure 2 is attractive, but needs some additional refinement.

1.1 Instead of sorting the mutations only by mutations type, the authors should try to sort them by phenotype and mutation type/localisation. To achieve this I suggest to fuse the figure and table together to one figure and to omit double information.

1.2 One possibility to give the reader a better overview without switching from table to figure is to present all mutations directly within the figure and use superscript numbers for references.

1.3 The phenotype could be for example be indicated by sorting mutations leading to BDE or an unclear phenotype above the exons and mutations leading to SPD below the exons.

1.4 Colour coding is not helpful as it cannot be discriminated in black and white prints. Shading (bold, italic, boxing etc) may be more helpful.

2. Title: Introduce „a“ before HOXD13: „Isolated Brachydactyly Type E Caused by a HOXD13 Nonsense Mutation: a Case Report“

3. Page 1, Line 4 : Exchange „has unknown genetic background“ with „the molecular pathogenesis has so far not been resolved“; i.e. the term „background“ relates to the overall genomic background i.e. SNPs etc.

4. Page 1, Line 5: Insert „the“: „Originally, the molecular cause...“

5. Page1, Line 6: The phrase „mutations in the HOXD13 gene product“ is somewhat confusing, omit „product“. The mutations take place on the DNA level within the gene, whereas the resulting consequences are found in the protein.

6. Page 1, Line 7: insert „one further “ in „...manuscript, one further HOXD13
mutation......“

7. Page 2, Paragraph 2, Line 6: insert „the“ in „Originally, the molecular cause“
10. Page 2, Paragraph 3, Line 9: The phrase „collection“ is not appropriate in this context. „Unpublished/own collection“ can be omitted as the data have been submitted to publication now.
13. Page 3, paragraph 4, line 6: The clinodactyly presented in the younger patient is one of the leading features (BDE is actually less prominent as correctly stated in the discussion). This fact should be pointed out by adding „resulting in rather severe clinodactyly......“
14. Page 4, Paragraph 2, Line 8: MLPA should be written out as „multiplex ligation-dependent probe amplification (MLPA)“
15. Page 4, Paragraph 3, Line 4/5 „f. e.“ is unclear and should be replaced by „i.e“. What do the authors mean by „at a second copy of the gene“ (this can be omitted).
16. Page 4, Paragraph 4, Line 1: The phrase „handful“ is not appropriate in the context of the presented topic concerning limb malformations.
17. Page 5, Paragraph 2, Line 4: The figure number is not mentioned.
18. Page 5, Paragraph 2, Line 5: Insert „the“: „end oft the homeodomain...“
19. Page 5, Paragraph 2, Line 6 „frameshifts“ should be replaced with „frameshift“ as it refers to „mutation“
20. Page 5, Paragraph 2, Line 13/14: „Hence,... mechanisms have been....“
21.-23. Page 9, Figure legends, Line 2, 10, 12: Start with a capital letter after „C-Clinical“, „H-Hand“ and „J-External“
24. Page 10, Table 2: Reference Column: Omit „ours“ as this is not appropriate. State in the table legend that the novel mutation described in this paper is printed in bold.

**Level of interest:** An article of importance in its field

**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.