Reviewer's report

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

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Reviewer: Georg Schwabe

Reviewer's report:

Jamsheer and colleagues describe a novel heterozygous nonsense HOXD13 mutation in a Polish female and her father with an isolated brachydactyly type E (BDE). Whereas HOXD13 alanine repeat expansions are associated with synpolydactyly, recently two missense mutations located in the HOXD13 homeodomain have been reported to lead to an overlapping BDD/BDE phenotype. The new aspect presented here by Jamsheer et al. is the heterozygous HOXD13 nonsense mutation that is predicted to result in a loss of the HOXD13 homeodomain leading to BDE.

Beyond the description of this interesting novel mutation, the presentation of the phenotype and the molecular data needs some refinement. In addition, only sparse background information on homeobox genes and limb development/malformation is offered. Furthermore, the authors need to better delineate their findings to previous data on HOXD13 mutations. Finally, the authors fail to discuss their findings in a broader, more functional and developmental context.

Major Compulsory Revisions

1. Phenotypic description

The phenotypic description of the limb malformation should be worked out in more detail and compared to the BDD/BDE phenotype, which is associated with missense mutations in the HOXD13 homeodomain. In addition to the fifth digit also other phalanges of the by Jamsheer et al. presented individual with BDE seem slightly deviated in the photographs and X-ray. Is a broad thumb characteristic for other forms of BDE or for patients with previously described HOXD13 mutations? In addition, it should be mentioned, that unlike in many other BDE cases, the metacarpals of the fourth digit of the individuals described by Jamsheer et al. are not particularly shortened.

2. Molecular analysis

2.1. PCR conditions should be listed. Primer sequences (and the size of PCR products) should be presented in the methods section, rather than being referred to only upon request.

2.2. In the chromatogram the predicted protein sequence and numbering of the codons should be added.
3. Genotype-phenotype analysis
This part would benefit from improvement, including a more precise genotype-phenotype delineation and additional background information.

3.1. The BDE and the SPD phenotype and their underlying mutations should be delineated more clearly. A figure indicating the novel and previously described HOXD13 mutations, their functional consequences and the resulting phenotypes should be introduced.

3.2. Are there examples for homeobox genes other than HOXD13, indicating that mutations affecting the homeodomain and alanine repeats lead to distinct phenotypes?

3.3. PTHLH mutations leading to BDE are mentioned in the introductory remarks. This idea may be resumed again in the discussion. Is there a molecular connection between HOXD13 and PTHLH?

3.4. A more general description of the role of HOX genes in limb development is lacking at the beginning and/or end of the report.

Minor Essential Revisions
1. It should be mentioned, whether other relatives without limb malformations exist. In addition, presentation of a pedigree, possibly together with the sequence chromatograms may be more illustrative.

Discretionary Revisions
1. Figure legend: Letters A - D in the figure legend should be in bould. Use B, C instead of B&C.

**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.