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

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Abstract: Brachydactyly type E (BDE; MIM#113300) is characterized by shortening of the metacarpal, metatarsal, and often phalangeal bones, and predominantly affects postaxial ray(s) of the limb. BDE may occur as an isolated trait or as part of a syndrome. Isolated BDE is rare and in the majority of cases has unknown genetic background. Originally, molecular cause of isolated BDE has been unravelled in 2 families and shown to result from heterozygous missense mutations in the homeodomain of the *HOXD13* gene product. Since the initial paper, *HOXD13* mutation has never been reported in a patient manifesting isolated BDE. In this paper, we report on a Polish family exhibiting isolated BDE caused by a nonsense heterozygous *HOXD13* mutation. We investigated a Polish female proband and her father, both affected by isolated BDE, in whom we identified a nonsense heterozygous mutation.
c.820C>T(p.R274X) in the \textit{HOXD13} gene. So far, only two missense \textit{HOXD13} mutations (p.S308C and p.I314L), localized within the homeodomain of the HOXD13 transcription factor were associated with BDE. Both changes were supposed to alter DNA binding affinity of the protein. The variant p.R274X identified in our proband is the third \textit{HOXD13} mutation, and the first truncating (nonsense) mutation reported to result in typical isolated BDE. Our case stands for the first evidence that truncating \textit{HOXD13} mutations can produce isolated BDE.

\textbf{Background}

Brachydactyly type E (BDE; MIM#113300) is characterized by shortening of the metacarpal, metatarsal, and often phalangeal bones, and predominantly affects postaxial ray(s) of the limb (1). In most cases BDE is syndromic and occurs within the clinical spectrum of Turner syndrome, Albright hereditary osteodystrophy (AHO; MIM#103580) or 2q37 deletion (1). Isolated BDE is rare and in the majority of cases has unknown genetic background. Originally, molecular cause of isolated BDE has been unravelled in 2 families and shown to result from heterozygous missense mutations in the homeodomain of the \textit{HOXD13} gene product (2). Missense variants affecting other residues of the C-terminal HOXD13 homeodomain may also give raise to different limb phenotypes such as synpolydactyly (SPD; MIM#186000) or syndactyly type 5 (MIM#186300), whereas expansion of the N-terminal HOXD13 polyalanine tract usually results in SPD (3-6). Recently, Klopopki et al. (7) described causative alterations (microdeletion and point mutations) in the \textit{PTHLH} gene in five unrelated families affected by isolated BDE. Since the initial paper of Johnson et al. from 2003 (2), \textit{HOXD13} mutation has never been reported in a patient manifesting isolated BDE. In addition, only 3 out of 12 annotated \textit{HOXD13} mutations resulted in a premature termination of the protein synthesis. Thus, genotype-phenotype correlation for truncating HOXD13 variants remains poorly known. In this paper, we relate on a Polish family exhibiting isolated BDE caused by a nonsense heterozygous \textit{HOXD13} mutation.

\textbf{Case presentation}

We investigated a Polish female proband and her father, both affected by isolated BDE. Skeletal manifestations of the proband (Fig. 1A & 1D) comprised shortening of the V\textsuperscript{th} right metacarpal, bilateral shortening and broadening of the I\textsuperscript{st} metacarpals, and bilateral shortening of the middle phalanges of V\textsuperscript{th} fingers with clinodactyly. Feet of the proband were clinically inconspicuous. The proband’s father (Fig. 1B & 1C) manifested shortening of the
V\textsuperscript{th} fingers and toes most probably due to shortened V\textsuperscript{th} metacarpals and metatarsals (no X-ray available). Both patients had normal stature and normal psychomotor development.

Genomic DNA was extracted from peripheral blood leukocytes according to salting-out method (8). The entire coding sequence of the \textit{HOXD13} gene (GenBank NM_000523.3) was amplified in PCR reactions and directly sequenced using dye-terminator chemistry. Primer sequences are available upon request.

The proband and her father carried a nonsense heterozygous mutation c.820C>T(p.R274X) in the \textit{HOXD13} gene (Fig. 1E). Presence of this mutation was excluded in 196 ethnically matched control chromosomes.

So far, only two missense \textit{HOXD13} mutations (p.S308C and p.I314L), localized within the homeodomain of the HOXD13 transcription factor were associated with BDE (2). Both changes were supposed to alter DNA binding affinity of the protein (2). The variant p.R274X identified in our proband is the third \textit{HOXD13} mutation, and the first truncating (nonsense) mutation reported to result in typical isolated BDE. The mutant HOXD13 protein synthesized in the proband is predicted to lack the entire homeodomain sequence and most probably cannot bind to DNA. All three previously described truncating \textit{HOXD13} mutations were frameshifts and produced a phenotype referred to as "SPD with foot anomalies" (MIM#186000), in which classic SPD was accompanied by supernumerary digit between I\textsuperscript{st}-II\textsuperscript{nd} and often IV\textsuperscript{th}-V\textsuperscript{th} metatarsals (9-10).

\textbf{Conclusions}

Our case stands for the first evidence that \textit{HOXD13} mutations that introduce premature stop codon can produce isolated BDE.

\textbf{Consent}

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

\textbf{Competing interests}

The authors have no competing interests to declare.

\textbf{Authors' contributions}

AJ - consulted the family, conceived the manuscript
AS - performed molecular testing of the patients and controls
LK - consulted the family of interest
ALB - critically revised the manuscript

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References


**Legends**

Figure 1. A - Brachydactyly type E (BDE) in the proband characterized by shortened Vth fingers, B & C - clinical picture of BDE (shortened Vth fingers and toes) in the proband's father, D - X-ray of the proband's hands showing shortening of the Vth right metacarpal, bilateral shortening and broadening of the Ist metacarpals, and bilateral shortening of the middle phalanges of Vth fingers (skeletal abnormalities are indicated by the white arrows), E - Chromatogram picture showing the c.820C>T(p.R274X) HOXD13 mutation.