Occurrence of Synpolydactyly and Omphalocele in a Fetus with a *HOXD13* Mutation

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Abstract

Keywords

- synpolydactyly
- *HOXD13*
- omphalocele
- syndactyly
- polydactyly

Synpolydactyly (SPD) is an autosomal dominant congenital limb disorder due to mutations in *HOXD13*. It is a phenotypically heterogeneous condition characterized by syndactyly of the third finger (F3), fourth finger (F4) and/or fourth toe (T4), and fifth toe (T5) with variably associated polydactyly. We report on a mother and fetus with SPD. The mother has a novel mutation (c.708_708delC) in the *HOXD13* gene that was also seen in the fetus. However, the fetus had congenital omphalocele in addition to SPD that is an association not reported to date. A chromosomal microarray in the fetus was normal. We report a novel mutation in *HOXD13* and document co-occurrence of an omphalocele and SPD in a fetus.

Introduction

Synpolydactyly (SPD; OMIM 186000) is an autosomal dominant congenital limb disorder caused by mutation in *HOXD13* (OMIM 142989). Typically, patients with SPD have syndactyly of the third finger (F3), fourth finger (F4) and/or fourth toe (T4), and fifth toe (T5) with variable expression and reduced penetrance.¹ Phenotypes may comprise pre-/post-axial polydactyly in the same or different digits. Metacarpal or metatarsal abnormalities can also be seen.

Clinical Report

A female fetus aborted at 17 weeks of gestation was referred for autopsy in view of multiple congenital anomalies. The mother was a primigravida in a nonconsanguineous marriage. There was no antenatal illness or exposure to known teratogens. Antenatal ultrasonography disclosed colpocephaly, a narrow thorax, and a large abdominal wall defect in the fetus. Clinical evaluation of the mother revealed bilateral cutaneous syndactyly of F3 and F4 (►Fig. 1A). Syndactyly was not present in the feet (►Fig. 1C). Radiographs of the mother showed partial fusion of distal phalanges of F3 and F4 as well as a bony growth on the medial side of proximal phalange of F4 on the right hand. There was complete duplication of the middle phalanges and partial duplication of the distal phalanges of F4 and synostosis of the proximal phalanges of F3, F4, and the third metacarpal on the left hand (►Fig. 1B). Partial duplication or spike-like bone growths from the proximal part of the second metatarsals were also noted (►Fig. 1D).

A detailed postmortem examination of fetus was performed. On external examination, an omphalocele was noted in the fetus with intestines, stomach, and liver present (►Fig. 2A, E). Bilateral complete cutaneous syndactyly of F3 and F4 was noted (►Fig. 2B, C). There was postaxial polydactyly of the left foot (►Fig. 2D). No other external or internal anomalies were present. Magnetic resonance imaging or autopsy of the brain could not be obtained due to autolysis. Radiographs of fetus hands were of poor resolution, inhibiting the ability to comment on phalangeal anatomy (►Fig. 2E).

We sequenced the *HOXD13* gene in both the mother and fetus. Sanger sequencing revealed a novel heterozygous deletion of c.708_708delC (p.N236Kfs*30) in exon 1 in both of them (►Fig. 3). However, the fetus has an omphalocele and SPD, which is an association not reported with *HOXD13*

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Fig. 1 Clinical photographs and radiographs of mother's hands (A, B) and feet (C, D) show bilateral cutaneous syndactyly of F3, F4 (A), partial fusion of distal phalanges of F3, F4 and bony growth on the medial side of proximal phalange of F4 on right hand (B), complete duplication of middle phalanges and partial duplication of distal phalanges of F4 and synostosis of proximal phalanges of F3 and third metacarpal of left hand (B). Clinically the feet appeared normal (C) whereas radiographs show partial duplication or spike-like projection from the second metatarsal (D). (Permission was obtained from the patient for publication.)

Fig. 2 Images show an omphalocele (A, E) in the fetus, bilateral cutaneous syndactyly of F3, F4 (B, C), and postaxial polydactyly of right foot (D). Radiograph shows an anteroposterior view of the fetus (E). (Permission was obtained from the parents for presentation.)

Fig. 3 Pedigree of the family by electropherograms (reverse sequence) shows heterozygous sequence variation, c.708_708delC (p.N236Kfs*30) in exon 1 of *HOXD13* gene in mother and fetus whereas father has normal sequence.

mutations in the literature.² SNP-based microarray was done to identify any copy number variants (CNVs) in the fetus due to the presence of the omphalocele. No pathogenic CNVs were found on SNP microarray. Chromosomal microarray was done in Illumina HumanCytoSNP-12 (resolution ~30 KB) platform (San Diego, California, United States). Analysis was performed by using Illumina KaryoStudio 1.4.3.0 Build 37 (CNV Plugin V3.0.7.0) software (San Diego, California, United States). We have excluded the CNVs not containing genes (unless associated with controlling elements of the genes with clinical significance), the regions not having any controlling elements, and those smaller than 0.2 Mb (unless associated with a gene of known clinical significance). Copy neutral LOH (loss of heterozygosity) was inferred by considering regions with clinical significance of greater than 8 Mb. The study has the approval of institutional ethics committee and informed consent was taken from the family for the study.

Discussion

We report on a fetus with SPD and omphalocele and SPD in the mother. Both had a novel pathogenic mutation in *HOXD13*. The mother has SPD in F3 and F4 whereas fetus has syndactyly of F3, F4, and polydactyly in a foot. This family demonstrates the variable presentation of this condition.

SPD is a clinically and genetically heterogeneous condition. Three genetically distinct types of SPD (SPD1

[*HOXD13*], SPD2 [*FBLN1*], SPD3 [14q11.2-q12]) have been described. Most reported cases are attributed to *HOXD13* mutations.³ Homeobox (*HOX*) genes encode transcription factors that are highly conserved and regulate the differentiation of body wall and limb axes in metazoans.⁴ *HOXD13* is present at the 5' end of the *HOXD* cluster that is the first *HOX* gene known to be linked to human developmental disorders. It is involved in patterning, differentiation and morphogenesis of limbs during development.⁵ Till date, 16 mutations in *HOXD13* are known to cause SPD.^{2,6} The most common variations among all known types of mutations in *HOXD13* are 15-residue N-terminal polyalanine repeats.⁷ In the present study, a novel frameshift variant, c.708_708delC in exon 1 of *HOXD13* was identified. The variant, c.708_708delC (p.N236Kfs*30) in exon 1 of *HOXD13*, identified in the proband, and affected mother introduces a premature termination codon leading to an abnormal transcript that is likely to result in either non-sense-mediated decay or formation of a truncated protein. *In-silico* tools such as MutationTaster ([prob: 1] [http://www.mutationtaster.org/]), SIFT Indel ([confidence score: 0.858] [http://sift.bii.a-star.edu.sg/www/SIFT_indels2.html]), and PaPI ([PAPI_Score- 0.862] [http://papi.unipv.it/index.xhtml]) predicted the variant to be pathogenic. This variant is not found in Exome Aggregation Consortium (ExAc) browser.⁸ Furthermore, loss of function variants in *HOXD13* are previously known to cause SPD.¹ This variant was not found in the father.

Mutations in *HOXD13* are also associated with brachydactyly type D (OMIM 113200), brachydactyly syndactyly syndrome (OMIM 610713), brachydactyly type E (OMIM 113300), and syndactyly type 5 (OMIM 186300). Mutations in polyalanine tract expansion in a mouse model (SPD homolog (*spdh*)) exhibits typical human SPD phenotypes,⁹ whereas targeted disruption of the *Hoxd13* homeobox in homozygous *Hoxd13* null mice demonstrates milder features of human SPD.¹⁰ However, omphalocele is not reported with *HOXD13* mutations in mice and humans.

Omphalocele is a midline defect in the anterior abdominal wall, and the mechanism of this defect is still not clearly known. It has been suggested that failure of the intestinal loops to reenter the abdominal cavity results in omphalocele. Another possibility is that omphalocele results from the failure of the embryonic lateral folds to fuse in the midline.¹¹ An omphalocele may occur as isolated condition or in association with other malformations. A single nucleotide polymorphism (SNP) array was performed to rule out the CNVs.

With this report, we would like to document the occurrence of omphalocele in a fetus with SPD with a frameshift mutation in *HOXD13*. It remains to be known whether any causal relationship exists.

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