Severe Form of Brachydactyly Type A1 in a Child with a c.298G > A Mutation in *IHH* Gene

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Abstract

Brachydactyly type A1 (BDA1) is characterized by short middle phalanges. We report the case of a child with a severe form of BDA1 with complete absence of the middle phalanges of all extremities. He had c.298G > A (p.D100N) mutation in *IHH* gene.

Keywords
- brachydactyly type A
- GDF5
- IHH

Introduction

Brachydactyly (BD) without extraskeletal manifestations is a group of skeletal disorders characterized by abnormal development of the metacarpals, metatarsals, and/or phalanges. BD was originally classified into five types (A–E) by Bell.[1] The condition was again reclassified by Fitch, Temtamy, and McKusick.[2,3] BD type A1 (BDA1) is characterized by a spectrum of phenotypes ranging from severe shortening or absence of the middle phalanges of the fingers and toes to the fusion of the middle and distal phalanges. Milder phenotypes involve hypoplasia of the middle phalanges in digits 2 and 5. Until now, mutations in *IHH* and *GDF5* genes have been reported to cause BDA1.[4–6] In this article, we report a severe case of BDA1 with missing phalanges in digits 2 to 5 of the hands and feet.

Case Report

A 5-month-old male presented with BD and joint laxity of the hands and feet (►**Fig. 1A–H**). He was the only child born to nonconsanguineous asymptomatic parents. There was no significant family history. He had a birth weight of 2.5 kg (standard deviation: –2). Initial examination was performed at the age of 5 months, reporting normal growth parameters with a length of 68 cm, head circumference of 42.5 cm, and weight of 6.5 kg. He was noted to have bilateral single interphalangeal joint creases. Radiographs of both his hands and feet revealed the absence of the middle phalanges of digits 2 to 5 (►**Fig. 2A–D**). There were no other skeletal abnormalities or systemic anomalies. The study protocol was approved by the institutional ethics committee at Kasturba Hospital in Manipal, and written informed consent was obtained from the participating patient. *IHH* and *GDF5* were sequenced from the blood samples obtained from the child. A known pathogenic variant, c.298G > A (p.D100N), in exon 1 of *IHH* gene was identified.[7] Sanger sequencing of parents did not reveal this variant, suggesting a *de novo* occurrence of the mutation.

Discussion

The locus 2q35-q37 responsible for BDA1 was identified in two large Chinese families. *IHH* gene within this locus was unraveled as one of the cause of BDA1.[4,5] Since then, eight mutations have been identified in 13 families.[5,7–14] Clinical features of patients with mutations in *IHH* gene are tabulated in ►**Table 1**. To date, only 13 families (88 affected individuals) with BD have been reported with mutations in *IHH* gene (►**Table 1**). The spectrum of severity associated with the variant c.298G > A (p.D100N) in *IHH* gene observed in this case and those previously reported cases could be due to variable expression.

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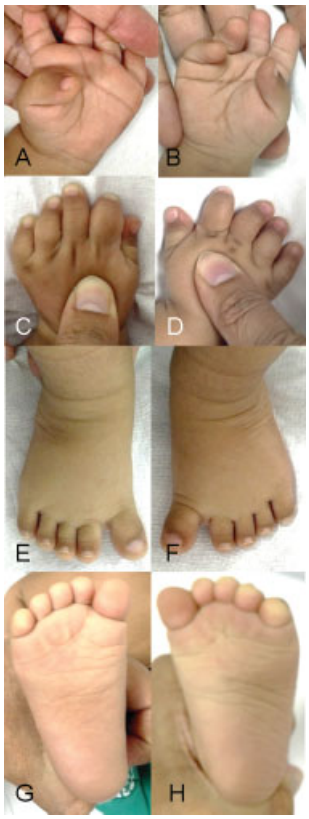

Fig. 1 (**A–H**) Photographs of hands and feet show brachydactyly. He has a single digital crease (**A,B**) and sandal gap deformity (**E,F**). Otherwise he is noted to have unremarkable extremities.

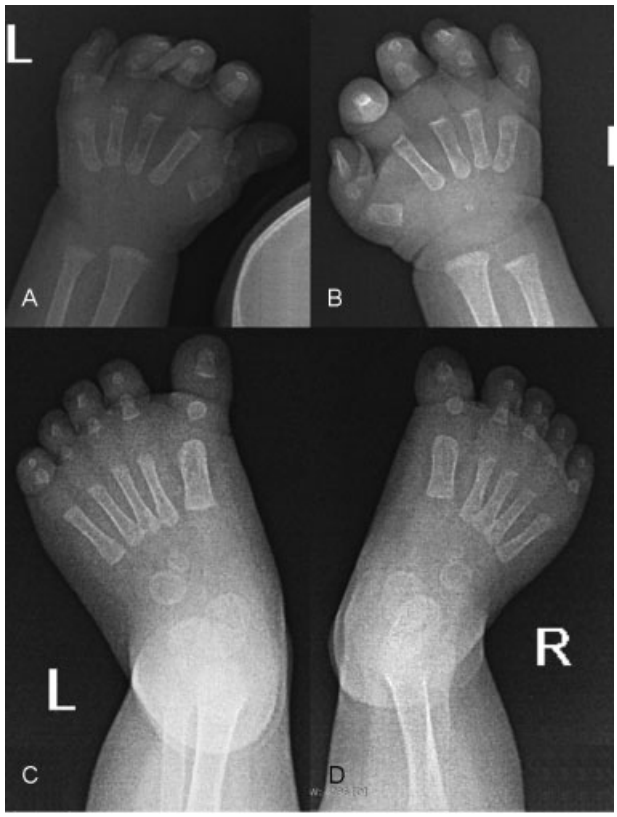

Fig. 2 Radiographs of the hands and feet show brachydactyly and missing middle phalanges of digits 2 to 5 in both the hands (**A,B**) and feet (**C,D**).

Table 1 Clinical features of patients with mutations in *IHH* gene

Serial no.	Total no. of family	No. of cases	Common features	Additional features	Mutation	Reference
1	1	10	Short middle phalanges of F2–F4; fused middle and terminal phalanges of F5	–	c.461C > T (p.Thr154Ile)	Liu et al[8]
2	2	5	Bilateral dysplasia of the carpals, metacarpals, and phalanges; absence of middle phalanges in F2, F3, and F5	Spurs on the trapezium; musculoskeletal problems such as pain in hip and knee	c.298G > A (p.Asp100Asn)	McCready et al[7]
		3	Broad hands and feet with hypoplasia or absence of middle phalanges in F2–F5 and short proximal phalanx of F1	Bilateral valgus deformity, double scoliosis, irregular femur, nystagmus, squint, developmental delay		
3	3	18	Variable phenotype of middle phalanges including absence of all middle phalanges or absence of middle phalanges F2, F4, and F5, or absence of middle phalanx F5	–	c.283G > A (p.Glu95Lys)	Yang et al,[4] Gao et al[5]
		15	Absence of middle phalanges; short middle phalanges in F2, F3, and F4; thin shafts and broad epiphyses in the metacarpals and proximal phalanges; short proximal phalanx of F1	Clinodactyly	c.391G > A (p.Glu131Lys)	

Table 1 (*Continued*)

Serial no.	Total no. of family	No. of cases	Common features	Additional features	Mutation	Reference
		5	Clinical phenotype of BDA1	–	c.300C > A (p.Asp100Glu)	
4	1	14	Broad and shortened digits; variable phenotypes of middle phalanges and metacarpal among affected individuals	–	c.298G > A (p.Asp100Asn)	Zhu et al[10]
5	1	3	Mild BDA1; broad and short digit of F1–F5	Absence or hypoplasia of the styloid process ulna	c.298G > A (p.Asp100Asn)	Giordano et al[12]
6	4	2	Short middle phalanges, prominent in F2 and F5; short proximal phalanx of F1	Short arms, restricted dorsiflexion of the feet, tarsal coalition	c.383G > A (p.Arg128Gln)	Byrnes et al[13]
		3	Short middle phalanges	Distal symphalangism, scoliosis, clubfoot	c.389C > A (p.Thr130Asn)	
		2	Short proximal and distal phalanges in F1	–	c.391G > A (p.Glu131Lys)	
		7	Absence of middle phalanges in F2–F5 in both hands and feet, short proximal phalanx in F1, syndactyly of F2 and F3	Nonspecific knee and hip problems, hallux vulga, absence of lateral incisors	c.298G > A (p.Asp100Asn)	
7	1	1	No details described	–	c.284A > G (p.Glu95Gly)	Kirkpatrick et al[9]
8	1	1	Absence of middle phalanges in F2–F5 in both hands and feet	–	c.298G > A (p.Asp100Asn)	Present case

Note: Hyphen indicates absence of data.

The most common phenotype observed is the absence of or short middle phalanges of digits. In some cases, additional features such as syndactyly, clinodactyly, spurs on the carpal bones, scoliosis, club foot, nystagmus, squinting, and developmental delay are also observed. In a French-Canadian family with BDA1, linkage analysis to 5p13.3–13.2 and sequence analysis of *IHH* gene did not reveal any pathogenic variation.[9] Mutation analysis in the patients of this family revealed a variant in *GDF5* gene.[6] Mutations in *GDF5* gene are known to cause BDA2 (OMIM: 112600) and BDC (OMIM: 615072). All of the preceding data suggests the presence of phenotypic heterogeneity and genetic heterogeneity in BDA1.

We report a severe form of BDA1 with missing middle phalanges of all digits in both the hands and feet. Reporting this c.298G > A (p.D100N) mutation in the family further validates the pathogenicity of the variant and indicates this is the most common variant in *IHH* gene. This report adds the phenotype of an infant to the literature.

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