

## Original Article

# Longitudinal Growth of the Short Bones of the Hand in a Girl with Pseudohypoparathyroidism Type Ia

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**Abstract.** Brachydactyly is a common feature of pseudohypoparathyroidism (PHP) type Ia. We studied the longitudinal growth of the short bones in the hand of a 15-yr-old girl with PHP type Ia who had been followed for congenital hypothyroidism. Radiographs of the hand of the patient, who had been X-rayed every year since 2 yr of age, were studied. She showed cone-shaped epiphyses of the hand at 2 yr of age before showing brachydactyly. At 4 yr of age, she showed brachydactyly and an advanced bone age, and some short bones were prematurely fused at 6 yr of age. The short bones without cone-shaped epiphyses were also short as a result of a disturbance of the longitudinal bone elongation. In conclusion, the brachydactyly of PHP type Ia is thus considered to be caused by both early epiphyseal fusion with cone-shaped epiphyses and a disturbance of the longitudinal bone elongation.

**Key words:** brachydactyly, longitudinal study, PHP type Ia, cone-shaped epiphyses, children

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## Introduction

Brachydactyly is the typical and most specific sign of Albright's hereditary osteodystrophy (AHO). This peculiar phenotype also includes short stature, obesity with a round face, subcutaneous ossifications and mental retardation. It has been described in many

subjects with pseudohypoparathyroidism (PHP) type Ia. Brachydactyly mainly involves the short metacarpals and metatarsals, especially the fourth and fifth, the short distal phalanx of the thumb and cone-shaped epiphyses (1). It is present in about 70% of PHP type Ia cases (2). Considerable variability occurs in the clinical and biochemical manifestations even among affected members in a single family (3). Very few reports have described when and how the typical skeletal features appear. We therefore studied the longitudinal growth of short bones in the hand of a girl with PHP type Ia who was followed for congenital hypothyroidism.

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## Case Report

The patient, 15-yr-old girl, had been followed for congenital hypothyroidism and she had been receiving thyroxine treatment. She was born at term after an uncomplicated fifth pregnancy. There was no evidence of consanguinity. Her birth weight was 2960 g and body length was 46 cm at 40 wk of gestation. Neonatal screening revealed an elevated thyrotropin level (TSH 33.2  $\mu$ IU/ml). At the age of 40 d, she showed a slightly elevated serum TSH (8.7  $\mu$ IU/ml) level with low-normal free thyroxine (1.3 ng/dl). On sonography the thyroid gland appeared normal. Treatment with levothyroxine (10  $\mu$ g/kg/day) was initiated for subclinical hypothyroidism. Although thyroid hormone substitution was sufficient (The TSH levels were almost normal range, levothyroxine dose was 6  $\mu$ g/kg/day at 1 yr of age), psychomotor development was mildly retarded. During follow-up, she gradually showed brachydactyly, obesity and short stature, and serum Ca levels were 8.4–9.1 mg/dl. Serum phosphorus and PTH were not measured. At 15 yr of age, further laboratory tests were carried out, to look for causes of AHO. Her height and weight at that time were 137.8 cm (–3.71 SD) and 51.8 kg, respectively. The percent of relative body weight excess was +28.9%. Her bone age was already adult. She had typical AHO with a round face, short neck, brachymetaphalangism and obesity. She had breast budding (Tanner stage III) but no menstruation. Both Chvostek's sign and Trousseau's sign were absent. The patient's biochemical and hormonal profiles are shown in Table 1. She had normocalcemia, normophosphatemia and increased serum PTH and gonadotropin levels. An Ellsworth-Howard test showed the absence of the expected rise in the urinary and plasma cyclic AMP (data not shown). We diagnosed her as having a PHP type Ia based on the clinical and laboratory findings, and the Ellsworth-Howard test. Subsequently, treatment with 1,25 dihydroxy vitamin D<sub>3</sub> was

**Table 1** Biochemical and hormonal characteristics at time of 100  $\mu$ g levothyroxine replacement

TSH	7.72 $\mu$ IU/ml	Ca	9.2 mg/dl
fT <sub>3</sub>	2.8 pg/ml	IP	4.6 mg/dl
fT <sub>4</sub>	1.3 ng/dl	intact PTH	370 pg/ml
LH	10.2 mIU/ml	%TRP	98.5 %
FSH	17.7 mIU/ml	IGF-1	180 ng/ml
E <sub>2</sub>	40 pg/ml	DHEA-S	393 ng/ml
BMD (Z score, L2–L4 DEXA)			–3.25 SD

BMD, bone mineral density; DEXA, dual energy X-ray absorptiometry; IP, inorganic phosphorus; %TRP, tubular reabsorption of phosphate; DHEA-S, dehydroepiandrosterone sulfate.

started. Family members underwent clinical and hormonal examinations, and the findings are shown in Table 2. The mother's siblings and parents showed neither short stature nor obesity. A DNA analysis of the patient was performed after obtaining informed consent. No mutation was identified in the coding exons and intron-exon boundaries of *GNAS1*.

## Materials and Methods

Radiographs of the hand of the patient, who had been X-rayed every year since two yr of age, were studied. The lengths of 19 tubular bones of the hand were measured to the nearest millimeter with a vernier caliper, and then compared to bone length standards (appropriate for age and sex) published by Matsuura *et al.* (4). (Japanese sample, birth to 17 yr). From these data, the number of standard deviations each of the hand bones deviated from the mean (the Z score) was determined. The bone age was estimated using the Japanese-standardized Tanner-Whitehouse 2 method and the bone morphology was evaluated based on the atlas of hand X-ray (5).

**Table 2** Clinical and hormonal findings of family members

	age (yr)	BH (cm)	BW (kg)	BMI	RF	SC	Br	MR	Ca (mg/dl)	P (mg/dl)	intact PTH (pg/ml)	TSH ( $\mu$ U/ml)	LH (mIU/ml)	FSH (mIU/ml)
normal range									8.7–10.0	2.5–4.6	10–60	0.6–4.1	*(1.1–18.3)*	*(3.4–13.9)
father	53	165	53	19.5	-	-	-	-						
mother	49	145	58	27.6	+	-	+	+/-	9.7	3.5	42	2.31	12.3	19.6
eldest sister	24	143.7	66.5	32.2	+	-	+	+	9.1	3.8	200	8.25	9.0	17.8
second eldest sister	23	141	68.6	34.5	+	-	+	+	8.5	5.1	280	12.01	13.6	14.4
third eldest sister	She died of heart failure at four months of age.											elevated TSH levels in neonatal screening		
fourth eldest sister	18	138.8	48.7	25.3	+	-	+	+	8.3	3.6	510	10.14	15.1	15.8

BH, body height; BW, body weight; RF, round face; SC, subcutaneous calcification; Br, brachydactyly; MR, mental retardation. \*, Normal values for follicular phase.

## Result

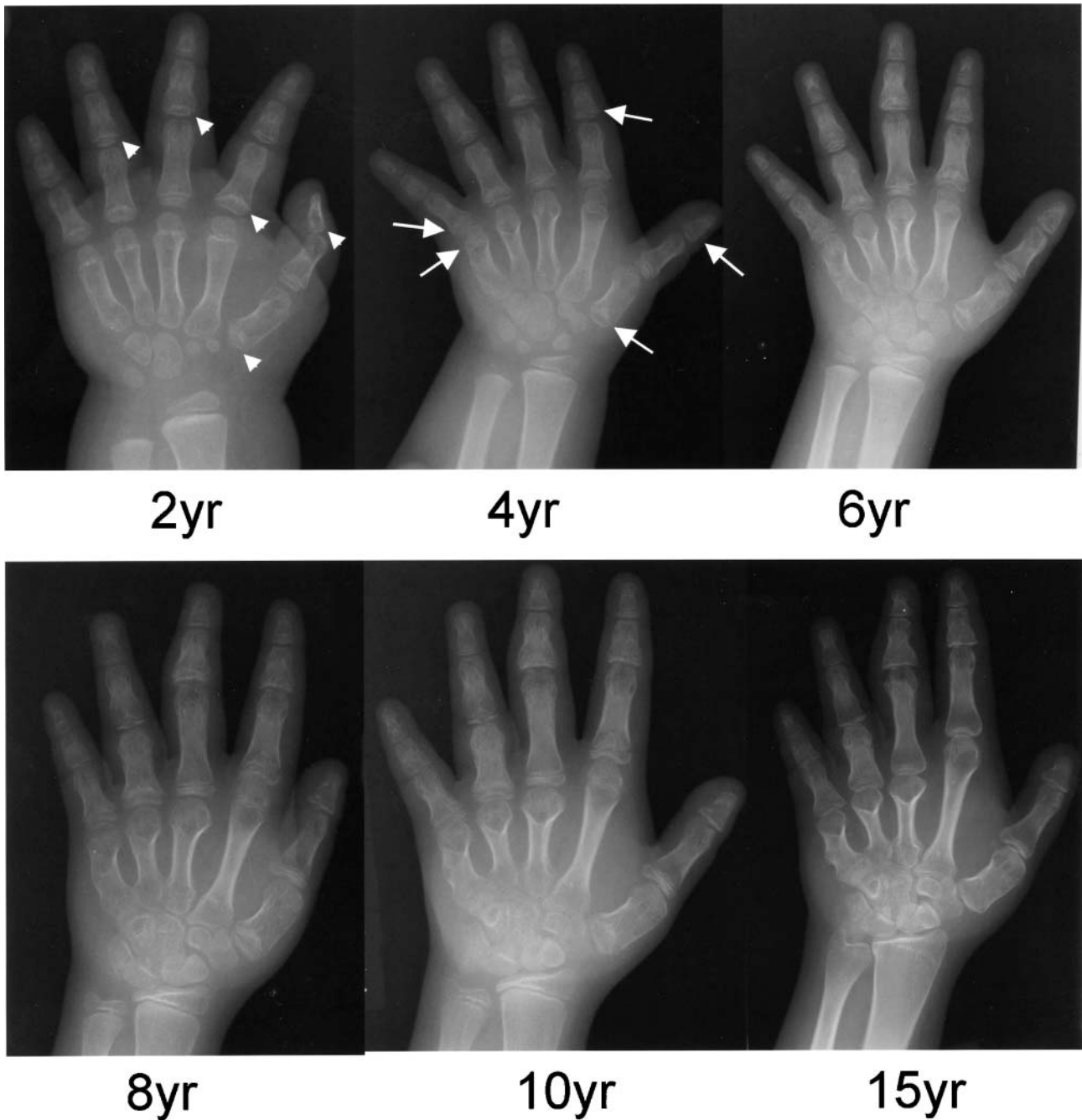
The longitudinal alterations of the left hand X-ray are shown in Fig. 1. The changes in the Z score of the short bones are shown in Fig. 2 and the Z score for each bone at 15 yr of age are shown in Table 3. The growth chart and bone age are shown in Fig. 3.

At 2 yr of age, no shortening of the bones was observed, however some bones showed cone-shaped epiphyses, the relative advancement of the carpals and the early fusion of the epiphyses (I, III, IV and V metacarpals; II, IV and V proximals; II, III, IV and V middle bones, all distal phalanges). At 4 yr of age, all distal phalanges and metacarpals except for the II distal phalange and the II metacarpal were found to show shortening below  $-2$  SDS. The most severely impaired segments were the I and V metacarpals, and the IV and V proximal phalanges (below  $-8$  SDS).

In some bones cone-shaped epiphyses were not clear, while longitudinal elongation was also disturbed and, as a result, they showed a shortening of the bones (II metacarpal, I and III proximal phalanges). Finally, shortening below  $-2$  SDS was found in all hand bones except for the I and III proximal phalanges.

## Discussion

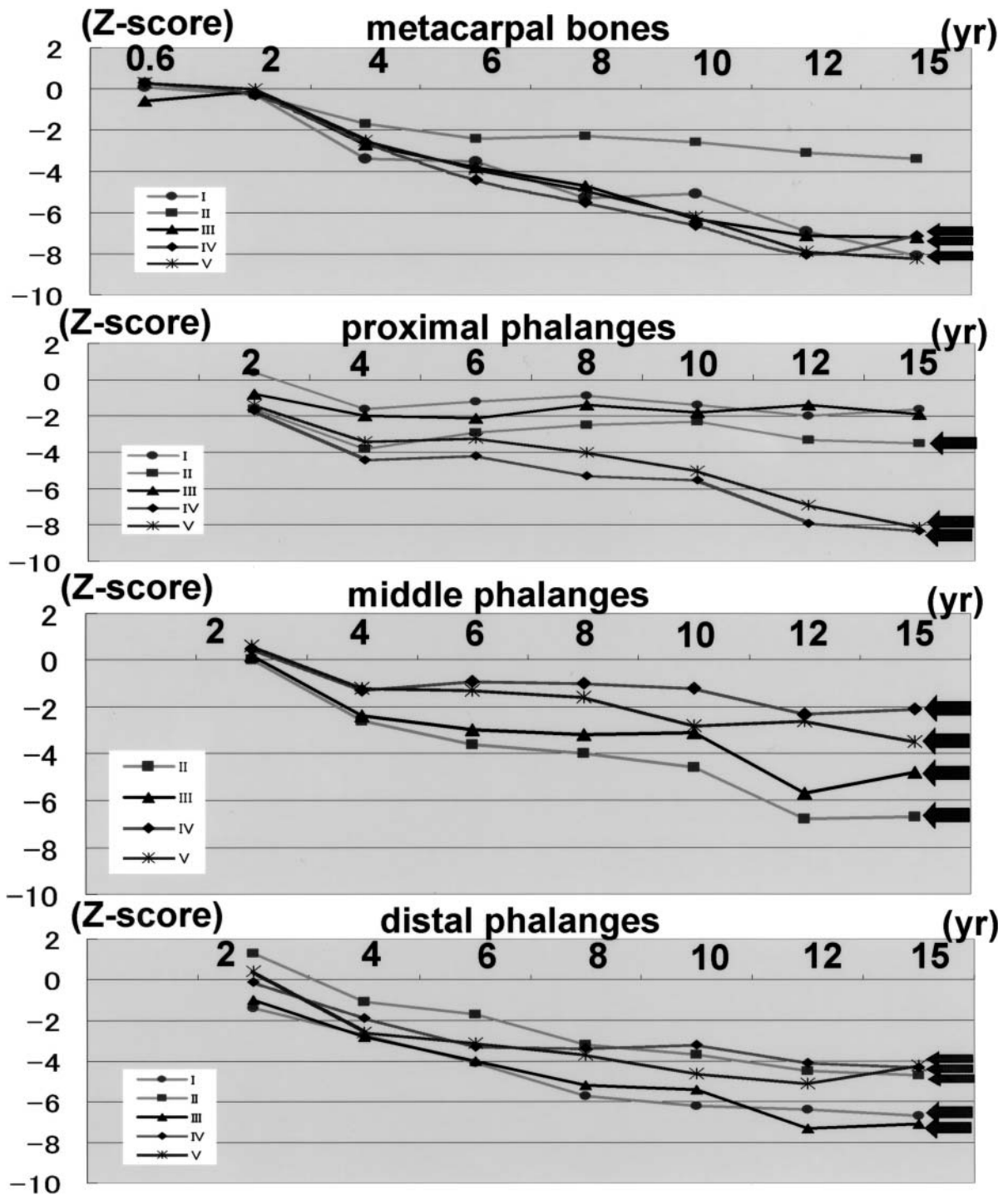
Subjects with PHP type Ia or pseudo PHP typically manifest a characteristic brachydactyly. However, so far, few reports have described when and how the typical skeletal features appear. By routine radiological examinations, a 70% brachydactyly prevalence was described in 20 PHP subjects by Merzoug *et al.* (2). Clinical or routine radiological examinations demonstrated brachydactyly in 11 of 14 patients (78.5%), and a metacarpophalangeal pattern profile analysis also revealed a significant shortening below  $-2$  SDS in one or more bones in all 14 subjects by de Sanctis *et al.* (6). The skeletal abnormalities of AHO may not be apparent until a child is 5 yr old (7). On the other hand, de Sanctis reported that typical bone features were observed even in a 3-yr-old child (6). Our longitudinal study showed no shortening of the hand bones to have existed at 2 yr of age, however, some bones showed cone-shaped epiphyses. Thereafter, at 4 yr of age, all distal phalanges and metacarpals except for the II distal phalanx and the II metacarpal demonstrated shortening below  $-2$  SDS. Great variability was observed in the bone-shortening entity (6), however, there were some cases who showed shortening of the bones by at least 4 yr of age.



**Fig. 1** Radiographs of longitudinal alteration of the left hand. Arrowheads indicate cone-shaped epiphyses and arrows indicate early fusions.

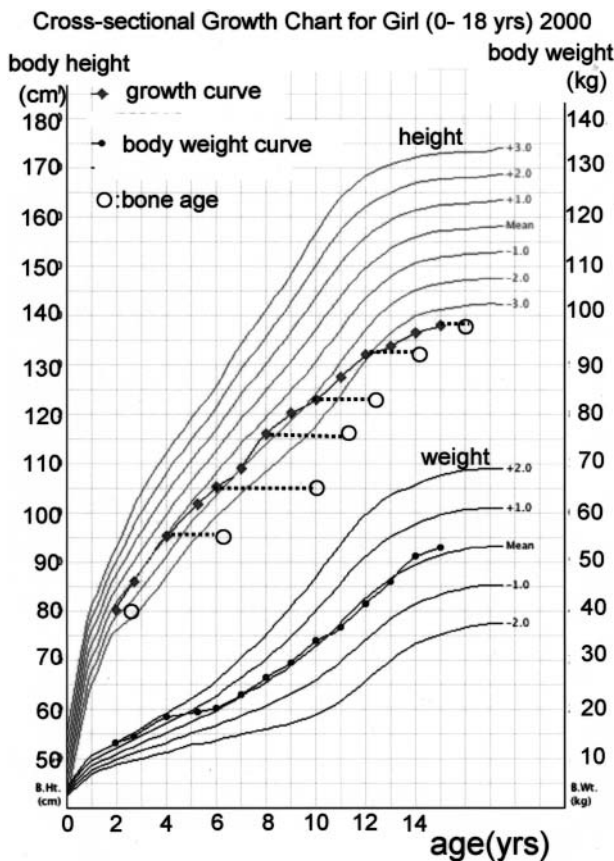
This shortening of the bones is often associated with early fusion with the cone-shaped epiphyses (7, 8). The etiology of PHP type Ia is unresponsiveness to the PTH/PTHrP receptor by

*GNAS1* gene mutation. The PTH/PTHrP receptor not only mediates PTH-dependent regulation of calcium and phosphate homeostasis but it also plays an important role in chondrocyte



**Fig. 2** Z scores of longitudinal alterations of short bones. Arrows indicate bones with cone-shaped epiphyses.





**Fig. 3** Growth chart. The open and closed circles, and closed diamond indicate bone age, body weight and body height, respectively.

proliferation and differentiation, and thus, also in bone growth and elongation (9). PTHrP prevents premature hypertrophic differentiation, thereby maintaining the length of the columns (9).  $Gs\alpha$  mutations in the proliferative layer of growth plate chondrocytes result in insufficient

PTHrP-dependent inhibition of chondrocyte maturation. Mantovani *et al.* reported that the clinical findings of osteodystrophy and obesity in PHP type Ia patients despite the presence of one normal  $Gs\alpha$  allele might be due to the presence of haploinsufficiency in this gene in both bone and adipose tissue (10). Therefore, PHP type Ia shows cone-shaped epiphyses and early fusion due to the insufficient inhibition of chondrocyte maturation, while also showing disturbance of longitudinal bone elongation due to shortening of the proliferative zone of growth plate chondrocytes. Our study shows that the short bones with cone-shaped epiphyses demonstrate severe shortening as a result of early fusion. The length of the metacarpal bones which showed cone-shaped epiphyses were shortened by about 4 SDS compared with the bones which did not. The short bones without cone-shaped epiphyses also demonstrated shortening as a result of disturbance of the longitudinal bone elongation. Finally, shortening below  $-2$  SDS was found in all hand bones except for the I and III proximal phalanges.

Brachydactyly has been described as a relative shortening and widening of specific hand bones, usually in the III, IV and V metacarpals and I distal phalanx (2). de Sanctis *et al.* reported that brachydactyly was identified in 14 genetically characterized PHP type Ia patients (6). The median Z scores indicated shortening below  $-2$  SDS in all metacarpals (ranging from  $-2.0$  to  $-3.5$  SDS) and all distal phalanges (ranging from  $-2.6$  to  $-4.5$  SDS), not only in the classically reported III, IV and V metacarpals and I distal

**Table 3** Z scores for each bone at 15 yr of age

	I	II	III	IV	V
metacarpal bones	-8.1	-3.4	-7.2	-7.1	-8.2
proximal phalanges	-1.6	-6.9	-1.9	-8.3	-8.1
middle phalanges		-6.7	-4.8	-2.1	-3.5
distal phalanges	-6.7	-4.7	-7.1	-4.3	-4.2

phalanx (6). The metacarpal and distal phalanges are relatively more impaired than other segments (6). In our case, many of the metacarpal and distal phalanges showed severe shortening below  $-4$  SDS. The most severely impaired segments were the I and V metacarpals, and IV and V proximal phalanges (below  $-8$  SDS). Great variability was observed in the bone-shortening prevalence between patients and between segments (6). The reason for the differences between segments is unclear.

In conclusion, cone-shaped epiphyses of the hand were observed at as early as 2 yr of age and before the presence brachydactyly was confirmed. At 4 yr of age, the patient demonstrated brachydactyly and an advanced bone age, while some bones had already fused. The short bones without cone-shaped epiphyses also demonstrated shortening as a result of disturbance in the longitudinal bone elongation. The brachydactyly of PHP type Ia is thus considered to be caused by both early epiphyseal fusion associated with cone-shaped epiphyses and disturbance of the longitudinal bone elongation. These findings will contribute to early recognition of PHP type Ia by hand X-ray.

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