

RESEARCH

Acrodysostosis and pseudohypoparathyroidism (PHP): adaptation of Japanese patients with a newly proposed classification and expanding the phenotypic spectrum of variants

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Abstract

Objective: This study aimed to report on 15 Japanese patients with acrodysostosis and pseudohypoparathyroidism (PHP) and analyze them using the newly proposed classification of the EuroPHP network to determine whether this classification system is suitable for Japanese patients.

Design: We divided the patients into three groups based on hormone resistance, the number of fingers with short metacarpals, the existence of cone-shaped epiphyses and gene defects.

Methods: We carried out clinical, radiological and genetic evaluations of two patients in group A (iPPSD5), six patients in group B (iPPSD4) and seven patients in group C (iPPSD2).

Results: Group A consisted of two siblings without hormone resistance who had the most severe bone and physical developmental delays. *PDE4D* gene defects were detected in both cases. Group B consisted of six patients who showed hormone resistance without hypocalcemia. Short metacarpal bones with corn-shaped epiphyses were observed in all patients. In two cases, *PRKAR1A* gene defects were detected; however, their clinical and radiological features were not identical. The facial dysmorphism and developmental delay were less severe and *PRKAR1A* gene defects were detected in case B-3. Severe facial dysmorphism and deformity of metacarpal bones were observed, but no gene defect was detected in case B-1. Group C consisted of seven patients with PHP1a, four of whom had maternally inherited heterozygous inactivating mutations in one of the *GNAS* genes. The clinical and radiological features of the patients in group C were not identical either.

Conclusions: The newly proposed classification is suitable for Japanese patients; however, heterogeneities still existed within groups B and C.

Key Words

- ▶ *PDE4D* gene defects
- ▶ *PRKAR1A* gene defects
- ▶ acrodysostosis
- ▶ *GNAS* gene
- ▶ pseudohypoparathyroidism

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Introduction

Acrodysostosis (ACRO) refers to a heterogenous rare skeletal dysplasia that shares characteristic features, including severe brachydactyly, facial dysostosis, cone-shaped epiphysis and nasal hypoplasia (1, 2, 3). The literature describing ACRO cases is confusing because some reported patients may have had other phenotypically related diseases, presenting with Albright hereditary osteodystrophy (AHO) such as pseudohypoparathyroidism (PHP) or pseudopseudohypoparathyroidism (PPHP) (1, 2, 3). There is a question as to whether patients do or do not display abnormal mineral metabolism associated with resistance to PTH and/or resistance to other hormones that bind G-protein-coupled receptors (GPCR) linked to G α , as observed in PHP1a.

The recent identification in patients affected with ACRO of defects in two genes, *PRKARIA* (1) and *PDE4D* (4), both important players in GRCP G α -cAMP-PKA signaling, has helped clarify some issues regarding the heterogeneity of ACRO, in particular, the presence of hormone resistance (1, 2, 3, 4, 5). Here, we present the *PRKARIA* and *PDE4D* gene defects and phenotypes identified in ACRO syndromes and discuss them in view of phenotypically related diseases caused by defects in the same signaling pathway (1, 2, 3, 4, 5). Large numbers of cases with PHP have been reported (6); however, only a small number of cases with *PRKARIA* (7, 8) and *PDE4D* (9, 10) in our country have been reported.

Short metacarpals are common in patients with ACRO, Turner syndrome, PHP and other congenital skeletal abnormalities (11). In the pediatric endocrine clinic, we usually take hand X-rays for the evaluation of bone age in patients with congenital hypothyroidism, pituitary dysfunction and various other diseases in which patients present with short stature.

During 50 years of clinical experience, we have had 15 cases of children with multiple short metacarpals, most of which were detected in patients with congenital hypothyroidism. On those occasions, we conducted radiological, endocrinological and genetic evaluations of these patients and compared them with the newly proposed classification.

Materials and methods

Fifteen patients with multiple short metacarpals were the subjects of this study (Table 1). They were divided into three groups (iPPSD2, 4, 5) based on a novel classification proposed by the EuroPHP network, (12) that is, hormone

Table 1 Clinical and biological features of the 15 cases with ACRO and PHP.

Group	Cases	Sex	Hypothyroidism	Hormone resistance	Hypocalcemia	Calcification	i-PTH (pg/mL)	Ca/P (mmol/L)	PTH loading	MR (IQ)	FT4 (T4)/TSH/TRH (max)
Group A	A-1	F	(-)	(-)	(-)	(-)	64.4	2.4/1.0	NE	Severe (54.3)	16.2/0.41
	A-2	M	(-)	(-)	(-)	(-)	61.7	2.3/1.1	NE	Severe (42.3)	16.1/1.25
Group B	B-1	M	(+)	(+)	(-)	(-)	54	2.3/1.5	NE	96	(42.5)/19.5/73.3
	B-2	M	(+)	(+)	(-)	(-)	150	2.4/1.5	Low resp	Mild	(76.0)/22.4/91.8
	B-3	M	(+)	(+)	(-)	(-)	170.9	2.3/1.8	Normal	Normal (105)	11.8/18.2/90.0
	B-4	F	(+)	(+)	(-)	(-)	437	2.2/1.8	Normal	Normal (105)	10.8/18.3/35.9
Group C	B-5	F	(+)	(+)	(-)	(-)	0.9**	2.2/1.6	Low resp	Normal (105)	14.2/13.2/59.2
	B-6	F	(+)	(+)	(-)	(-)	138	2.4/3.1	Normal	Mild	16.7/20.3/91.0
	C-1	M	(+)	(+)	(-)	(-)	110	2.2/1.6	Low resp	Light (70)	10.1/23.4/65.6
	C-2	F	(+)	(+)	(-)	(-)	17	2.3/1.7	Normal	Light (70)	12.9/19.24/91.8
	C-3	M	(+)	(+)	(+)	(+)	436	1.8/2.5	Low resp	Light	(88.9)/14.3/NE
	C-4	F	(+)	(+)	(+)	(+)	0.45**	2.0/2.4	Low resp	Light	(77.3)/4.0/46.0
	C-5	M	(+)	(+)	(+)	(+)	435	1.3/2.7	Low resp	Light	4.8/19.8/119.9
C-6	F	(+)	(+)	(+)	(+)	380	2.1/1.4*	Low resp	Light	9.6/61.2/154.4	
C-7	F	(+)	(+)	(+)	(+)	120	2.4/1.9*	Low resp	Light	12.9/28.7/32.0	

Serum Ca normal range, 2.2–2.7 mmol/L; serum P, 1.3–1.85 mmol/L; serum FT4, 7.5–15.0 pmol/L; serum total T4, 58–140 nmol/L; i-PTH, 10–65 pg/mL.

*On vitamin D; **PTH-C.

MR, mental retardation.



resistance, thyroid function, hypocalcemia, the number of fingers with short metacarpals (three or more) and the existence of cone-shaped epiphyses. If pathogenic variants in the responsive genes are detected, this has priority over clinical signs.

Group A consisted of two patients (siblings) without hormone resistance whose thyroid function and serum Ca levels were normal. Multiple short metacarpals (three fingers or more) and cone-shaped epiphyses were observed. Pathogenic variants in the *PDE4D* (4) were detected in some of the cases.

Group B consisted of six patients with hormone resistance, multiple short metacarpals (two fingers or more) and cone-shaped epiphyses whose thyroid function was impaired and serum Ca levels were normal. Pathogenic variants in *PRKAR1A* (1) were detected in some of the cases.

Group C consisted of seven patients with PHP who exhibited hormone resistance and typical AHO whose thyroid function and serum Ca levels were impaired except in cases C-1 and C-2. Short metacarpals were observed only in fingers IV–V, except in case C-1, and cone-shaped epiphyses were not observed except in case C-1. Pathogenic variants in the *GNAS* gene were detected in some of the cases.

Thyroid functions were evaluated by the TRH loading test (5 µg/kg) and PTH loading test, with i.v. injection of 125 U/m² of synthesized 1–45 PTH, using methods previously described (13). Genetic analysis was conducted by exome sequencing, using a method previously described (10). The exome data were analyzed to detect not only single nucleotide variants (SNVs) and indels but also copy number variants (CNVs) in the genes. The cases were collected over the past 50 years of clinical experience, so the methods used for the evaluation of hormone levels, particularly serum parathyroid hormone levels and free thyroid hormone levels, were not necessarily identical. Radiographic evaluation of hands was based on the numbers of short metacarpals and cone-shaped epiphyses.

Obesity was defined as BMI of more than 25 for those who had completed puberty. For younger children, it was based on the method described by Ito (14).

The definition of SGA was based on that of The Japanese Society for Pediatric Endocrinology (15), that is, both birth weight and height of less than the 10th percentile of sex- and gestational-age-matched controls and either birth weight and height of less than –2 s.d. of sex- and gestational-age-matched controls. The data for birth height are listed in Table 2; however, many data for height were lacking. Many doctors did not stretch the legs of infants, particularly, low birth weight infants, at birth for fear of deleterious effects on hip joints.

Table 2 Clinical biological, radiological and molecular profiles of the 15 cases of ACRO and PHP.

Group	Cases	Sex	Gestational (weeks)	Birth weight (kg)	Birth length (cm)	Shortness metacarpals	Corn-shaped epiphysis	Family history	Round face/obese	Gene	Variant
Group A	A-1	F	40	2.3	46.0	II–V	II–V	(+)	–/–	<i>PDE4D</i>	NM_001104631:c.683A>C;p.(Q228P)
	A-2	M	40	2.2	46.0	II–V	II–V	(+)	–/–	<i>PDE4D</i>	NM_001104631:c.683A>C;p.(Q228P)
Group B	B-1	M	39	2.1	45.0	II–V	II–V	(–)	–/+	ND	
	B-2	M	39 weeks + 4 days	2.3	NA	II–V	V	(–)	–/+	NE	
Group C	B-3	M	37 + 6 days	1.8	42	IV–V	V	(–)	–/–	<i>PRKAR1A</i>	NM_002734:c.593G>A;p.(Q198E)
	B-4	F	42	2.4	NA	II–V	II–V	(–)	–/–	NE	
	B-5	F	40	3.4	NA	III–V	IV–V	(–)	–/–	NE	
	B-6	F	30 + 5 days	0.64	31.0	II–V	II–V	(–)	–/+	<i>PRKAR1A</i>	NM_002734:c.1004G>C;p.(R335P)
	C-1	M	39 + 4 days	2.7	46.0	III–V	IV–V	(+)	+/+	<i>GNAS</i>	NM_000516:c.493C>T;p.(R165C)
	C-2	F	40	2.9	37.5	IV–V	(–)	(–)	+/+	ND	
	C-3	M	NA	NA	NA	IV–V	(–)	(–)	+/+	NE	
C-4	F	40	3.5	NA	IV–V	(–)	(–)	+/+	NE		
C-5	M	36 + 2 days	2.3	NA	IV–V	(–)	(+)	+/+	ND		
C-6	F	36 + 2 days	2.8	47.5	IV–V	(–)	(+)	+/+	ND		
C-7	F	40 + 3 days	2.9	46.0	IV–V	(–)	(+)	+/+	+/+	<i>GNAS</i>	NM_000516:c.863T>A;p.(I288N)

NA, not available; ND, not detected; NE, not examined.

Bone age was evaluated by the Japanese standardized Tanner-White second (RUS) method (16).

Ethical approval and genetic analysis

The genetic study was approved and performed in two places. The first was from the Ethics Committee for Human Genome Research and Analysis of the Graduate School of Medicine, University of the Ryukyus (approved on July 1, 2014 (No. 73) and August 5, 2014 (No. 96)), where Dr Tadashi Kaname was then working. Genetic analysis was conducted by exome sequencing using a method previously described (10).

The second was from Institutional Review Board of Keio University School of Medicine (December 18, 2014 (No. 20140289)). Direct sequencing for coding exons and their splice sites of *PRKARIA*, *PDE4D*, *GNAS*, *GATA3*, *GCM2*, *PTH*, *AIRE*, *CASR*, *GATA3* and *GCM2* genes was analyzed (9). All blood samples were obtained after receiving written informed consent from the patients or their parents.

Informed consent was obtained from five patients or parents for the pictures of faces in this paper.

Results

Figures 1, 2, 3 and Tables 1, 2 summarize the clinical, laboratory, genetic and radiographic findings of the 15 patients in this report.

Brief clinical characteristics of each group

Group A (iPPSD5)

The two patients (siblings) in this group exhibited the most severe deformities of facial and hand bones and were reported previously (10, 17). Multiple short metatarsal

bones and cone-shaped epiphyses were observed in both cases. Genetic analysis was performed and revealed a pathogenic variant (NM_001104631:c.683A>C;p.(Q228P)) in the *PDE4D* gene (10) (Table 2). Their final body sizes were 149.1 cm, 54.3 kg, BMI 24.4 for A-1 and 135.0 cm, 42.3 kg, BMI 23.2 for A-2, respectively. The IQs of A-1 and A-2 were 54.3 and 42.3, respectively, and they were the most severely impaired patients in this series. Both were SGA infants.

Group B (iPPSD4)

This group consisted of six patients. All of them exhibited multiple short metatarsal bones, cone-shaped epiphyses, hypothyroidism and normal serum calcium and phosphorus levels, although serum iPTH levels were elevated compared to the normal level in all cases except B-1 and B-5. None of the patients exhibited CNS calcification. Two cases had pathogenic variants in the *PRKARIA* gene (Table 2). Five of the six cases exhibited shortening of metacarpal bones in fingers II-V or III-V but in B-3, who had a *PRKARIA* pathogenic variant, only in fingers IV-V (Fig. 2).

Group C (iPPSD2)

The seven patients in this group were diagnosed with PHP type 1a. Three cases were sporadic and the remaining four cases (C-5 and C-6 were siblings) were familial (C-1, C5-C7). Two patients had pathogenic variants in the *GNAS* gene (C-1 and C-7) (Table 2). The mothers of four, C-1, C-5, C-6 and C-7, with familial cases, had the same diseases.

None of patients exhibited cone-shaped epiphyses except in case C-1 (Fig. 3) and shortening of metacarpals was observed in fingers IV-V, except for case C-1, in which it occurred in fingers III-V. Hypocalcemia was not found

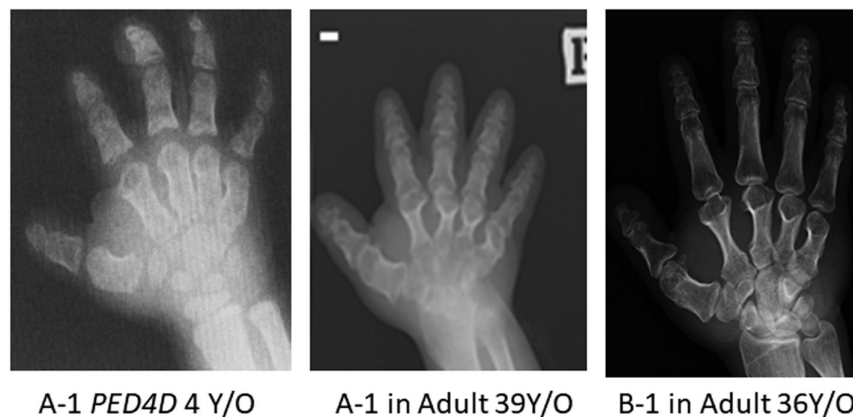
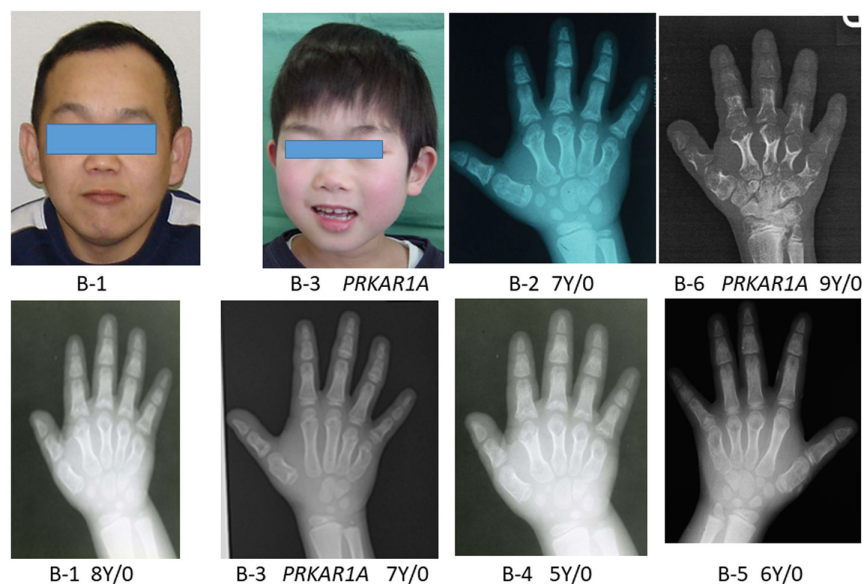


Figure 1

Hand X-rays of patients A-1 in childhood and adulthood and B-1 in adulthood. Unlike in B-1, there is severe shortening of metacarpal and phalangeal bones and cone-shaped epiphyses in case A-1, in which a *PDE4D* pathogenic variant was detected.

**Figure 2**

Photographs of face and X-rays of the hands of patients in group B. Shortening of metacarpal bones and cone-shaped epiphyses in fingers II–V is observed in all patients except B-3, with such shortening only in fingers IV–V, in whom a *PRKARIA* pathogenic variant was detected.

in cases C-1 or C-2. CNS calcification was found in all cases except C-1 and C-2. AHO was detected in all cases. Ectopic calcification was observed in four familial cases (C-4 to C-7).

Hormone resistance and hypothyroidism

Serum TSH and Ca levels were in the normal range in group A, in which hormone resistance did not appear. Serum iPTH levels in A-1, A-2 were 64.4 and 61.7, respectively, and were in the upper normal range (normal range: 10–65 pg/mL). On the other hand, serum TSH and PTH levels were elevated and an exaggerated response to TRH was observed in groups B and C (Table 1). Hormone resistance was present in groups B and C.

Shortness of metacarpals and cone-shaped epiphyses

Multiple short metacarpals (fingers II–V) and cone-shaped epiphyses were observed in cases of groups A and B, except for case B-3. In that case, there were short metacarpals in fingers IV–V and a pathogenic variant in *PRKARIA* was diagnosed. Hand X-rays for adult cases A-1 and B-1 are shown in Fig. 1. Although the cone-shaped epiphyses and shortness of metacarpals looked similar in cases A-1 and B-1 in childhood, these signs differed in adulthood, being more prominent with phalangeal bones also involved in case A-1.

Six of the seven cases in group C had shortness of metacarpal bones only in fingers IV–V. The exception was

case C-1, with shortness of metacarpals in fingers III–V and a cone-shaped epiphysis in finger V in early childhood. This case was considered to belong to group-B at first; however, a *GNAS* pathogenic variant was detected, and PHP 1a was diagnosed. The same findings were observed in the mother of C-1.

Serum calcium and PTH levels

Serum electrolyte levels when they were in their 30s, including calcium and phosphorus, and intact PTH (iPTH) were normal in cases A-1 and A-2. Although serum calcium and phosphorus were in the normal range in group B patients (B-1 and B-2 were in their 30s, and the remaining four were teens), serum iPTH was elevated in all six patients except in B-1 and B-5. Serum calcium levels were decreased in all patients except C-1 and C-2 in group C. Hypocalcemia and convulsions developed in early infancy and were treated with vitamin D in cases C-6 and C-7 at the age of 2 days. CNS calcification was observed in all cases except C-1 and C-2. The mother of C-1 had the same clinical characteristics as C-1.

Small for gestational age infants

Information on the birth lengths of cases B-2 and B-4 was lacking. However, the birth weights of both were below –2 SD of sex- and gestational-age-matched controls and they were diagnosed as SGA. Therefore, all patients in groups A and B were SGA except B-5. In contrast, all patients in group C were adequate for gestational age infants.

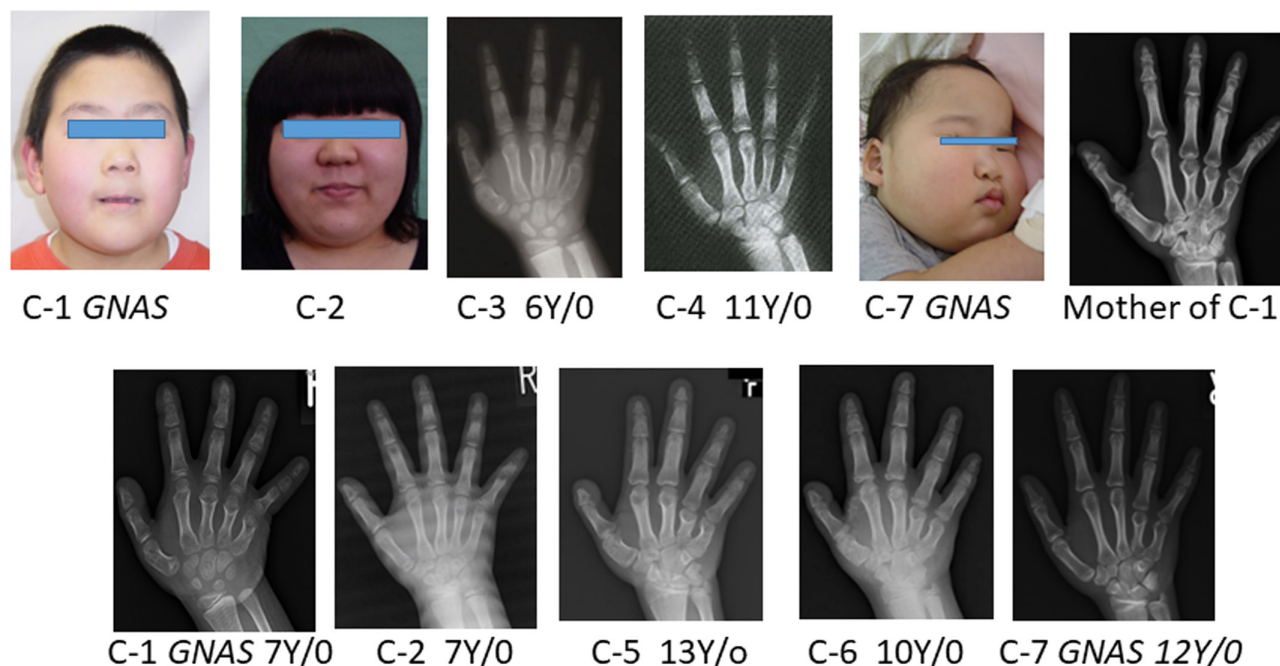


Figure 3

Facial photographs and X-rays of the hands of patients in group C. Shortening of metacarpal bones in fingers II–V can be seen in all cases except C-1 and his mother. Shortening of metacarpal bones in fingers III–V and cone-shaped epiphyses can be observed in C-1, in whom a *GNAS* pathogenic variant was detected. The serum Ca level was in the normal range and no CNS calcification was observed in patient C-1, his mother or in C-2.

Mental retardation

Both patients in group A showed severe mental retardation, whereas the patients in groups B and C were normal or only mildly retarded.

PTH loading test

This test was not done in group A due to the finding of no hormone resistance. In three of the five cases in group B, there were normal responses to PTH, and in two of these three cases, a *PRKARIA* pathogenic variant was detected. Six patients in group C underwent the PTH loading test, but only C-2 showed a normal response.

Genetic analysis

Genetic analysis was performed by whole exome sequencing (WES) analyses, which could detect SNVs, indels and CNVs, as previously reported (10), and the direct sequencing method as previously described (10). Cases in which pathogenic variants were detected are listed in Table 2. For cases B-1 (proband of this study), pathogenic variants in *GNAS*, *PDE4E* and *PRKARIA* were not detected by WES analyses. Epigenetic analysis was not performed.

Auxological data and SDS of the 15 cases of ACRO and PHP at diagnosis

Auxological data at diagnosis are provided in Table 3. The most recently diagnosed cases were in group C, who were diagnosed during infancy due to conversion due to hypocalcemia, familial occurrence and other anomalies.

Discussion

Here, we have reported 15 cases with shortening of metacarpal bones and a distinctive face with or without hormone resistance. The literature describing ACRO and its related diseases is confusing. The EuroPHP network proposed a novel reclassification of ACRO and PPHP to inactivate PTH/PTHrP signaling disorders (iPPSD) in nine forms (12). Group A would be classified into iPPSD5, group B into iPPSD4 and group C into iPPSD2 according to the new classification.

We divided our 15 cases into 3 groups according to the clinical features. Group A consisted of two cases, siblings, who were previously reported (10, 17). They exhibited no hormone resistance and the most severe shortness of metacarpals and pharyngeal bones. Although serum electrolytes were in the normal range, iPTH was in the high

Table 3 Auxological data and SDS of 15 cases of ACRO and PHP at diagnosis.

Group	Cases	Sex	Age at diagnosis (years)	Height (cm)	SD at diagnosis	Weight at diagnosis (kg)	SD at diagnosis	Pubertal stage (tanner)	Bone age at diagnosis (years)
Group A	A-1	F	2 8/12	90.4	-0.8	12.0	-1.7	I	-
	A-2	M	7/12	68.0	-0.6	0.8	-0.6	I	-
Group B	B-1	M	8 5/12	111.3	-2.9	25.0	-0.5	I	7 3/12
	B-2	M	5 1/12	94.5	-3.2	14.5	-1.0	I	3
	B-3	M	7 5/12	106.5	-3.3	15.0	-2.1	I	6 9/12
	B-4	F	5 1/12	97.6	-2.0	15.5	-1.0	I	5 6/12
	B-5	F	6 0/12	109.5	-1.1	21.8	0.7	I	6 1/12
	B-6	F	11 9/12	132.2	-2.5	34.5	-0.5	I	14
Group C	C-1	M	7 3/12	113.0	-1.8	27.0	0.8	I	7 9/12
	C-2	F	7 2/12	123.5	0.8	38.0	0.0	I	6 5/12
	C-3	M	6 1/12	NA	NA	NA	-	I	6
	C-4	F	11 1/12	130.0	-1.9	46.5	1.7	II	10 7/12
	C-5	M	2 9/12	86.0	-1.6	15.5	0.2	I	-
	C-6	F	2 days	46.0	-1.1	2.9	-	I	-
	C-7	F	1 11/12	78.0	-2.0	13.5	1.0	I	-

NA, not available; ND, not detected; NE, not examined.

normal range. Most cases with *PED4D* showed no hormone resistance; however, Michot reported cases with PTH resistance (4). A-1 and A-2 lived in a facility for the disabled in the city of Abashiri in Hokkaido, which has heavy snowfall during winter and where many children suffer from rickets in winter. Their high normal iPTH levels may have been related to mild vitamin D deficiency, although serum Ca, P and ALP were in the normal ranges. Serum 25-(OH)D was not measured this time. They also exhibited the most severe mental and physical developmental delays. They had pathogenic variants in *PDE4D* and were definitely different from the patients in groups B and C.

Group B consisted of six patients with hormone resistance who were diagnosed during hand X-rays for evaluation of congenital hypothyroidism, except for case B-1. All six patients had a distinctive face, short stature, shortness of metacarpal bones and cone-shaped epiphyses. None of the six exhibited clinical signs of hypocalcemia and their serum calcium and phosphorus levels were within normal ranges, although their iPTH levels were all higher than normal except for cases B-1 and B-5. CNS calcification was not observed in these patients. The PTH loading test was performed on five patients and three of them showed normal responses. Of these three, two had pathogenic variants in *PRKARIA*, but gene analysis was not done for case B-4. Hand X-rays of these three cases were quite different from each other. Case B-3 showed shortness of metacarpals only in fingers IV-V, which was similar to the report by Linglart (5). In contrast, case B-6 had the most severe bone deformities,

which was very similar to cases reported by Linglart (1, 5) and Muhn (3).

The pattern of shortening of the bones of the hand was reported by Poznanski (11), who compared short metacarpal bones in patients with PHP, PPHP, Turner syndrome, ACRO and brachydactyly type E. However, the diagnoses of these patients depended only on the PTH loading test, and no other biological data are available. The pattern profiles of the bones in patients with PHP, PPHP and ACRO were almost identical. They emphasized the use of metacarpal sign to evaluate the relative shortening of the fourth metacarpal, common in cases with Turner syndrome and PHP; however, in some cases of PHP, there are metacarpal sign negative PHP patients whose third metacarpal is short as in case C-1 (11).

Graham *et al.* (18) also reported radiographic comparisons of ACRO and PHP. They emphasized spinal stenosis and the severe shortening of metacarpal bones. Spinal stenosis was not evaluated in our cases, but the severity of shortening of metacarpal bones and cone-shaped epiphyses was observed in our cases, particularly, in case B-1. However, the severity of the metacarpal bone shortening was not identical in group B. Case B-3 had the mildest deformities and short metacarpal bones only in fingers IV-V. This finding was also observed in a case reported by Linglart (5). In contrast, very severe deformities were observed in B-6, though both cases had pathogenic variants in *PRKARIA*. Group B would be classified into iPPSD4; however, the cases were not identical and not all exhibited pathogenic variants in *PRKARIA*.

Among the seven cases in group C, two (C-1 and C-7) had maternally inherited heterozygous inactivating variants in one of the *GNAS* genes, as did their mothers. As far as their clinical findings are concerned, the cases would have maternally inherited heterozygous inactivating variants in one of the *GNAS* genes (C-1, C-5-C-7), although *GNAS* pathogenic variants were not detected in C-5 or C-6.

The clinical features of these four cases differed. Cases C-5 to C-7 exhibited typical clinical features of PHP1a; that is, hypocalcemia, CNS calcification, a round face, obesity and short metacarpals in fingers IV-V. Case C-1, however, did not show hypocalcemia or CNS calcification. Short metacarpals were found in fingers III-V and cone-shaped epiphyses were also observed. These findings were the same as in his mother. The PTH loading test showed low responses in all eight cases examined except C-2. Short metacarpals found in fingers III-V were also reported by Nagasaki (19), whose case also exhibited normal serum Ca and phosphate levels, with cone-shaped epiphyses observed in early childhood. Truelove (20) reported two adult cases with PHP and ACRO whose serum Ca levels were normal. *GNAS* and *PRKARIA* gene defects were detected in both of the patients and suggested the existence of subtypes of this disorder. Usardi (21) reported 20 cases of PHP 1a (iPPSD2) with an inactivating mutation on the maternal allele of *GNAS*. They found that serum Ca, but not phosphate, decreased with age at 4 years of age. They reported the mutation type and biological data; however, they did not show the shortening of metacarpal bones or other biological data for these cases.

Case C-2 had a clinical picture different from the others. This case showed typical features of AHO but with a normal serum Ca level and no CNS calcification. The PTH loading test showed normal phosphorus excretion and cAMP generation. We would like to perform more detailed gene analysis in this case.

The newborn infants in seven of the eight cases in groups A and B were SGA infants, a finding that was also reported previously (1, 2, 4, 5, 8, 19). On the other hand, all newborn infants in group C were adequate for gestational age infants.

In summary, we reported 15 patients with ACRO and PHP 1a. The cases of ACRO without hormone resistance or *PDE4D* pathogenic variants were quite different from those in the other groups from the clinical and radiological standpoints. In contrast, the cases having ACRO with hormone resistance and a *PRKARIA* pathogenic variant were not identical. Not all clinically identical cases had a *PRKARIA* pathogenic variant like case B-1. Radiological findings of cases with a detected *PRKARIA* pathogenic

variant were not identical either, like cases B-3 and B-6. Viewed from a different angle, Michot *et al.* suggested expanding the phenotypic spectrum of variants between *PDE4D* and *PRKARIA* (22).

The clinical and radiological features of group C were not identical either. Case C-1 had shortness of metacarpals observed in fingers II-V and had no hypocalcemia or CNS calcification, quite different from the remaining cases in group C. It is not clear at present whether these differences were due to the type or site of mutation or other reasons. Pediatric endocrinologists should pay careful attention to shortness of metacarpal bones and corn-shaped epiphyses when taking hand X-rays.

Although a new classification has been proposed by Thiele (12), clinical, radiological and genetic heterogeneities still existed. Recently, Elli *et al.* reviewed the literature on pseudohypoparathyroidism, acrodysostosis and progressive osseous heteroplasia, and the major and minor features of the diseases and their specificities, as well as the overlap associated with the most frequent subtypes (23). In the future, however, we have to collect more cases describing detailed clinical, laboratory, radiological and genetic features.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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