

## Case Report

# Endocrinological and phenotype evaluation in a patient with acrodysostosis

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**Abstract.** Acrodysostosis is characterized by distinctive facial features and severe brachydactyly. Mutations in *PRKAR1A* or *PDE4D* are known to be responsible for this disease. Cases of hormonal resistance have been reported, particularly in patients with *PRKAR1A* mutations. The physical characteristics and endocrine function of pseudohypoparathyroidism type Ia is known to resemble acrodysostosis. We report the case of a 4-yr-old patient with a *PRKAR1A* mutation. He had characteristic facies with an upturned nose and cone-shaped epiphyses of most phalanges. These findings have not been reported as extensive for cases of pseudohypoparathyroidism type Ia. He also had TSH resistance from birth. We performed endocrinological stimulation tests to further evaluate his endocrine status. These examinations revealed resistance to TSH and PTH, but there was normal secretion of ACTH, GH, and cortisol. An Ellsworth-Howard test resulted in normal urinary cAMP excretion. This response differs from that of pseudohypoparathyroidism type Ia. In summary, the constellation of an upturned nose, cone-shaped epiphyses of most if not all phalanges, and PTH resistance with a normal urinary cAMP response may satisfactorily enable clinical diagnosis of acrodysostosis.

**Key words:** acrodysostosis, upturned nose, cone-shaped epiphysis, urinary cAMP, *PRKAR1A*

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## Introduction

Acrodysostosis (ACRDYS) is a rare skeletal dysplasia characterized by severe brachydactyly,

midface hypoplasia, and developmental retardation. Recently, mutations in *PRKAR1A* or *PDE4D* were found to be responsible for this disease (1, 2). Hormonal resistance is associated with ACRDYS in some cases (1, 3–6). However, few patients with genetically diagnosed ACRDYS have undergone endocrinological stimulation tests.

Pseudohypoparathyroidism type Ia (PHP Ia) is characterized by multihormone resistance, rounded face, nasal hypoplasia, and brachydactyly of mainly the fourth and fifth metacarpals. There is a substantial overlap between the clinical features of ACRDYS and PHP Ia. Differentiating

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Received: November 3, 2016

Accepted: March 10, 2017

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**Table 1.** Thyroid function tests before  $LT_4$  administration

Day after birth	6	14	21	28
TSH ( $\mu$ IU/mL)	27.38	31.55	17.46	21.94
fT <sub>4</sub> (ng/dL)	1.39	1.54	1.14	1.02
fT <sub>3</sub> (pg/mL)	2.14	2.37	2.5	2.9

these diseases may be problematic in patients with atypical and/or subtle manifestations. One potential means to circumvent this problem may be genetic analyses. However, at present, genetic testing is not widely available. In this study, we aimed to identify the features that are specific to ACRDYS and are different from PHP Ia. To this end, we performed a comprehensive analysis of the clinical features and endocrine function of our case as well as a comprehensive review of the published literature.

### Case Report

The patient was a 4.2-yr-old boy. He was born at 37 wk and 3 d of gestation. He was small for gestational age (SGA). At birth, his length was 43 cm ( $-2.39$  SD) and his weight was 1941 g ( $-1.92$  SD). Neonatal mass screening revealed elevated serum TSH. Subsequent thyroid function tests revealed persistently elevated TSH (Table 1). Owing to these results,  $LT_4$  was initiated from d 28.  $LT_4$  was increased according to his TSH levels, but administration of 4  $\mu$ g/kg/d  $LT_4$  did not normalize his TSH levels. He was referred to our hospital for further evaluation at the age of 2.4 yr.

Our patient had no developmental delay (head control at 4 mo, rolled over at 6 mo, sat without support at 8 mo, could stand alone at 13 mo, and combined words at 29 mo). He had a history of recurrent otitis media. There were no other family members with endocrinological disease.

At 4.2 yr of age, his height and weight were 94.8 cm ( $-1.65$  SD) and 14.7 kg ( $+0.79$  SD), respectively. He exhibited midface hypoplasia,



**Fig. 1.** Radiograph of the left hand at 4.2 yr of age. Arrows designate cone-shaped epiphyses of the phalanges.

upturned nose, epicanthal folds, brachydactyly, and simian creases. His radiographs showed short metatarsals and metacarpals and cone-shaped epiphyses in all phalanges (Fig. 1). His bone age was estimated to be at 3.9 yr. His karyotype was 46,XY.

Analysis of data from laboratory tests revealed increased serum PTH (102 pg/mL; normal range 9–65 pg/mL) and normal serum calcium (9.9 mg/dL; normal range: 8.8–10.8 mg/dL) and phosphate (5.6 mg/dL; normal range: 3.7–5.6 mg/dL) levels. His free T<sub>4</sub> was 1.6 ng/dL (normal range: 0.8–2.2 ng/dL), free T<sub>3</sub> was 380 pg/dL (normal range: 230–660 pg/dL), and TSH was 2.66  $\mu$ IU/mL (normal range: 0.7–6.4  $\mu$ IU/mL) with 40  $\mu$ g/day  $LT_4$  administration. His free T<sub>4</sub> and free T<sub>3</sub> remained unchanged after TRH stimulation. TSH showed a normal response under  $LT_4$  treatment. The insulin tolerance test demonstrated normal GH, ACTH, and cortisol secretion. Gonadotropin-releasing hormone

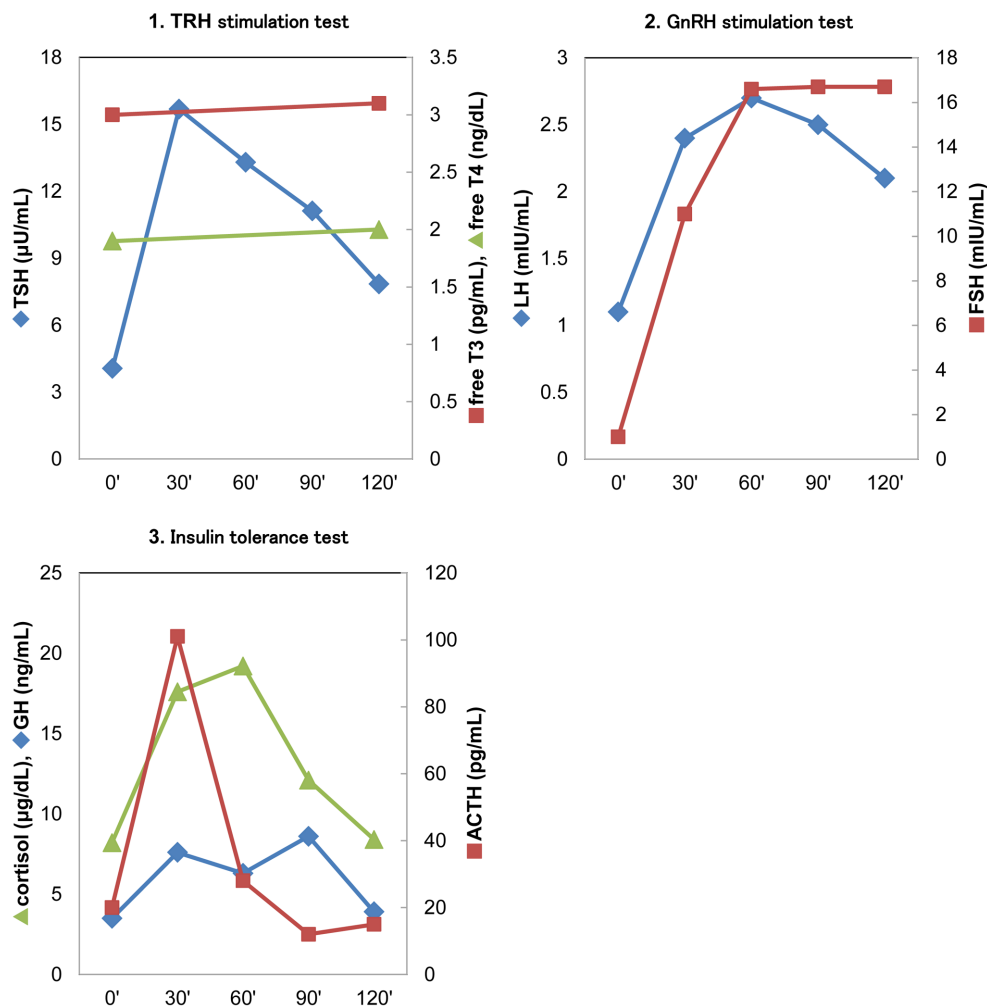


Fig. 2. Results of the (1) TRH stimulation test, (2) GnRH stimulation test, and (3) Insulin tolerance test.

Table 2. Ellsworth-Howard test

		Patient	Normal response	
Urinary cAMP excretion before and after PTH infusion	(0 min~60 min) – (–60 min~0 min)	5.85	> 1	μmol/hr
	(0 min~60 min) / (–60 min~0 min)	21.04	> 10	
Urinary phosphate excretion before and after PTH infusion	(0 min~120 min) – (–120 min~0 min)	22.53	> 35	mg/2 hr

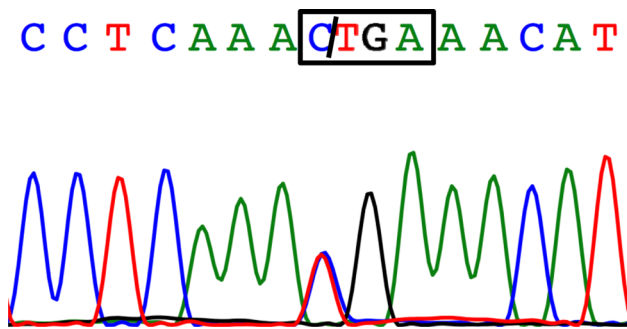
(GnRH) stimulation resulted in prepubertal gonadotropin levels (Fig. 2).

Normal urinary cAMP but subnormal phosphate excretion was observed with the PTH infusion test (Table 2). Since he had

brachydactyly and PTH resistance, ACRDYS with resistance to TSH was suspected.

After obtaining informed consent, a genetic analysis was performed. DNA was extracted from peripheral WBCs. Exons of the *PRKARIA*

gene were amplified with PCR and were directly sequenced using Big Dye Terminator version 3.1 (Thermo Fisher Scientific K.K. [Applied Biosystems], Yokohama, Japan). Both strands were analyzed to confirm the sequence. The *PRKARIA* gene analysis revealed a previously reported nonsense mutation in exon 11 (c.1102C>T; p.R368\*), confirming the diagnosis of ACRDYS (Figs. 3 and 4).



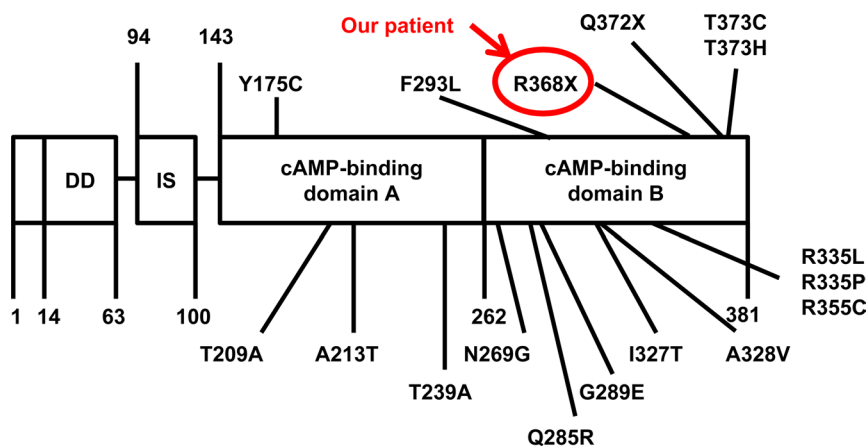
**Fig. 3.** Automated sequencing trace for *PRKARIA* shows a heterozygous cytosine-to-thymidine substitution (c.1101C>T) (indicated in the black box), corresponding to a stop codon replacing the arginine at position 368 (p.R368X).

## Discussion

We report the case of a boy with ACRDYS. His clinical features (midface hypoplasia, upturned nose, and brachydactyly) and hormonal resistance were suggestive of a diagnosis of ACRDYS with hormonal resistance. His endocrinological stimulation tests showed resistance to PTH and TSH and normal secretion of ACTH and GH. Because he was prepubertal, gonadal function was difficult to evaluate. Gene analysis revealed a known *PRKARIA* mutation.

Common features of ACRDYS are broad face, low nasal bridge, upturned nose, brachydactyly, and cone-shaped epiphyses. Linglart *et al.* previously examined 16 cases of ACRDYS and reported that all patients showed typical facial and peripheral dysostosis (broad face with widely spaced eyes, maxillonasal hypoplasia, severe brachydactyly, and cone-shaped epiphyses) (3). Our patient had an upturned nose, brachydactyly, and cone-shaped epiphyses, which is typical of ACRDYS. He also had epicanthal folds. This is not a typical finding but is listed in Online Mendelian Inheritance in Man (OMIM) (7).

PHP Ia is characterized by a round face with a flattened nose, short metacarpals (especially the fourth and fifth metacarpals), and ectopic



**Fig. 4.** Schematic diagram of *PRKARIA*. Numbers indicate the amino acid residues at the domain boundaries. The p.R368X mutation has been reported in 16 cases including ours (1, 3–6, 10). DD; dimerization domain, IS; inhibitory site.

ossification. It can be difficult to differentiate ACRDYS diagnosis from that of PHP Ia because many features, including brachydactyly and hypoplastic nose, are shared between these diseases. However, while an upturned nose is seen in 97% of ACRDYS patients, it is not described in PHP Ia (7, 8). A PubMed search yields only one case report of PHP Ia with cone-shaped epiphyses, but this trait appeared in only five phalanges in this case (9). Thus, the upturned nose and cone-shaped epiphyses of most (if not all) phalanges may be important features to distinguish ACRDYS from PHP Ia.

Another feature of our patient was SGA. He was born at 37 wk of gestation and his height and weight were 43 cm ( $-2.39$  SD) and 1941 g ( $-1.94$  SD), respectively. Four reports have previously described the relationship between ACRDYS and SGA or intrauterine growth restriction [IUGR]. Of the two cases reported by Wilson *et al.*, one of them was SGA (10). Elli *et al.* examined previously reported ACRDYS cases and found that 15% of the cases with *PRKAR1A* mutations had IUGR (5). Michot *et al.* found that two of the eight reported cases had IUGR (2). Linglart *et al.* reported that 11 of the 14 reported cases of ACRDYS were SGA (3). SGA is defined as birth weight and/or length below the 10th percentile or  $-2$  SD from the mean (11). However, the majority of the above-mentioned reports do not completely list birth weight, height, or gestational age, making it difficult to confirm whether the patients were truly SGA or not. Taking into consideration that the incidence of SGA in the general population is 2.3–10% (11–13), we suspect that SGA is a characteristic feature of ACRDYS. Accumulating more precise data should clarify whether the prevalence of SGA is increased in ACRDYS. On the other hand, since 41% of PHP Ia patients were born SGA (14), this feature may be limited in its use as a distinguishing trait while differentiating the two diseases.

Hormonal resistance is seen in both ACRDYS and PHP Ia. Elli *et al.* reported that patients

with *PRKAR1A* mutations more frequently demonstrate hormonal resistance (PTH: 76%; TSH: 73%; FSH: 18%), compared with patients with *PDE4D* mutations (PTH: 27%; TSH: 8%; FSH: 19%) (5).

Our patient showed TSH resistance from birth. Following TRH infusion, he showed a normal TSH response, but no increase in free T<sub>3</sub> or free T<sub>4</sub> was observed, confirming TSH resistance. The patient also showed increased PTH levels despite normal serum calcium and phosphate levels, indicating PTH resistance. The Ellsworth-Howard test demonstrated a quick rise in urinary cAMP but no significant change in urinary phosphate levels, indicating a defect downstream of cAMP. Linglart *et al.* and Elli *et al.* have also reported similar findings (1, 5).

An age-appropriate response was obtained for the GnRH tolerance test in our patient. However, the results were difficult to interpret because the patient was prepubertal. Linglart *et al.* also performed a GnRH stimulation test in two adult male patients. The response to GnRH was normal in both cases (1).

Normal GH, ACTH, and cortisol responses to the insulin tolerance test was also observed. Nagasaki *et al.* and Muhn *et al.* described a normal GH response to the GHRH stimulation test (4, 6). ACTH/cortisol secretion in ACRDYS has not been studied to date. Our results indicate an intact hypothalamus-pituitary-adrenal axis. However, a limitation of this report is that the results are from a single case.

In summary, the physical and endocrinological features of ACRDYS were evaluated. Since features of PHP Ia and ACRDYS are similar, it can be difficult to differentiate between these diseases. Although gene analysis will confirm the diagnosis, we searched for simpler approaches that can be performed at the bedside. The physical features observed, particularly in ACRDYS, are upturned nose and cone-shaped epiphyses in most, if not all, phalanges. The Ellsworth-Howard test induces cAMP secretion in ACRDYS, but not in PHP

Ia. In addition, we show that ACTH/cortisol secretion is normal in ACRDYS.

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