

# Variable degree of hormonal resistance in patients with Progressive Osseous Heteroplasia

Kentaro Miyai, Noriko Nishina, Masaki Takagi, Masahiro Goto and Yukihiro Hasegawa  
Tokyo Metropolitan Children's Medical Center, Division of Endocrinology and Metabolism

## Background

Progressive Osseous Heteroplasia (POH) is characterized by heterotopic ossifications (HO) in a deep muscle and fascia. To date, *GNAS1* gene loss-of-function mutations on paternal allele were reported as responsible for POH. Unlike other *GNAS1* related diseases such as pseudohypoparathyroidism 1a (PHP1a) or pseudopseudohypoparathyroidism (PPHP), patients with typical POH do not show hormonal resistance (HR) or Albright hereditary osteodystrophy (AHO). But some patients diagnosed as POH with HR and/or AHO were reported previously as overlapping syndrome with POH/PHP1a or POH/PPHP.

## Objective

The aim of this study is to investigate the degree of HR in four patients with clinically diagnosed as POH in our hospital.

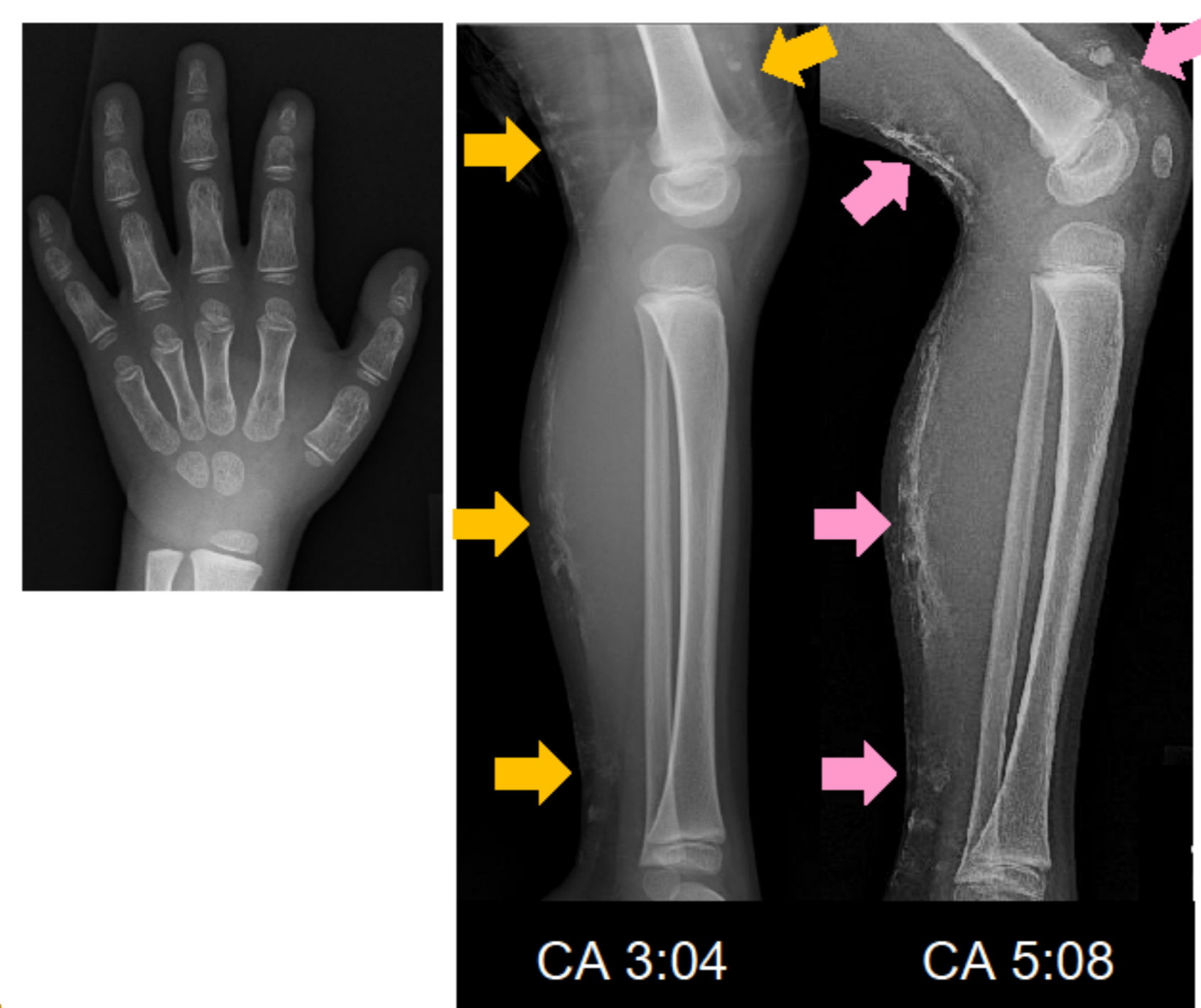
## Case presentations

**patient 1** 14-years-old boy  
【Clinical diagnosis】 POH  
【Birth】 37w, 1700g, 42cm  
【Past history】 n.p.  
【Family history】 n.p.  
【Clinical history】  
Heterotopic ossification was noticed at the right sole at the age of one year (→). Another one was noticed at the right elbow at the age of six years (→). He shows no signs of AHO. Hormonal resistance has not been observed.



**patient 2** 6-years-old boy  
【Clinical Diagnosis】 POH/PPHP  
【Birth】 35w0d, 1694g, 45.6cm  
【Past history】 n.p.  
【Family history】 n.p.  
【Clinical history】 Heterotopic ossifications were noticed at the left calf and left hand in infancy, and became large gradually. Short stature and brachydactyly was pointed out at the age of three. Transient increase of PTH was observed without abnormalities in Ca, P and thyroid function during the age of four years.

CA	3:10	4:01	4:04	4:07	4:10	6:01
iPTH (pg/mL)	50.2	104.6	85.1	65.6	35.6	39
Ca (mg/dL)	9.8	9.6	9.7	9.6	9.5	9.2
P (mg/dL)	5.1	5.5	5.7	4.6	4.7	4.3



**patient 3** 12-years-old girl  
【Clinical diagnosis】 POH/PHP1a  
【Birth】 37w5d, 1252g, 36cm  
【Past history】 n.p.  
【Family history】 n.p.  
【Clinical history】  
Heterotopic ossification at left heel was noticed during infancy and removed at the age of five years. Short stature, learning difficulty, brachydactyly and obesity was noticed at the same time. Persistent elevation of PTH without abnormalities in Ca, P and thyroid function was observed from the age of eight years. The heterotopic ossification at left heel was recurred at the age of ten (→) and removed again at the age of twelve.

CA	8:02	9:03	10:03	10:07	11:08
iPTH (pg/mL)	95.8	77.4	101.4	162.8	85
Ca (mg/dL)	9.9	10.0	9.8	10.3	10.0
P (mg/dL)	4.1	4.9	4.1	5.2	4.4



**patient 4** 6-years-old boy  
【Clinical diagnosis】 POH/PHP1a  
【Birth】 38w3d, 3152 g, 50 cm  
【Past history】 undescended testes (bil.)  
【Family history】 n.p.  
【Clinical history】 Hypothyroidism was pointed out by newborn mass screening (TSH 30.0 μIU/ml, fT4 1.12 ng/dl) and treatment with LT4 was started. Heterotopic ossification at right calf was noticed at the age of four years (→). Another heterotopic ossification was detected at right shoulder (→). Mental retardation, brachydactyly and obesity were noticed. Elevation of PTH with hypocalcemia (intact-PTH 562 pg/ml, Ca 8.3 mg/dl) was detected at the age of five years and treatment with alfacalcidol was started.



## Summary of the patients

The phenotypic variances and genetic analyses of the patients are summarized in the table below.

Patient	1 <sup>1)</sup>	2	3	4
Clinical Diagnosis	POH	POH/PPHP	POH/PHP1a	POH/PHP1a
HO	+	+	+	+
HR	-	PTH (transient)	PTH	PTH, TSH
AHO	-	Short stature Brachydactyly	Short stature Brachydactyly Obesity, LD	Brachydactyly Obesity MR
Birth	37w 1700g	35w0d 1694g	37w5d 1252g	38w3d 3152g
<i>GNAS1</i> mutation	c.1027C>T (exon 12)	c.565_8delGACT (exon 7)	c.432+1G>A (IVS 5)	c.368G>T (exon 5)
inheritance	de novo	de novo	de novo	de novo
Parental origin of the allele with mutation	paternal	under investigation	under investigation	under investigation

## Discussion

- Patient 1 could be diagnosed as typical POH phenotypically and genetically<sup>1, 2)</sup>.
- Patients 2, 3, 4 show hormone resistance and signs of AHO with variable degree, thus diagnosed as POH overlapping with PHP1a or PPHP, similar to the cases reported previously<sup>3-6)</sup>.
- It seems that Patient 4 shows characteristics that patients with PHP1a often show except for HO. On the other hand, patient 2 and 3 shows only mild (compensated) hormone resistance different from those observed with PHP1a patients.
- These variances observed in hormone resistance as well as AHO might be explained by other than *GNAS1* mutation.

## References

- 1) Goto M, et al. J Pediatr Endocrinol Metab 2010; 23:303-9
- 2) Shore EM, et al. N Engl J Med 2002; 346:99-106
- 3) Kaplan FS, et al. J Bone Miner Res 2000; 15:2084-94
- 4) Adegbite NS, et al. Am J Med Genet A 2008; 146A:1788-96
- 5) Lebrun M, et al. J Clin Endocrinol Metab 2010; 95:3028-38
- 6) Elli FM, et al. Bone 2013; 56:276-80

Disclosure statement: We have nothing to disclose.  
This work was supported by JSPS KAKENHI Grant-in-Aid for Young Scientists(A) Grant Number 15K21681