

# A girl with Beckwith-Wiedemann syndrome (BWS) and pseudohypoparathyroidism type 1B (PHP1B), a unique example of multiple imprinting defects

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## Conclusions

- Multiple imprinting defects can cause multiple diseases in patients.
- Symptoms of PHP1B may be absent at time of diagnosis of BWS.
- As prolonged subclinical hypocalcaemia can have negative consequences (intracerebral calcifications, cardiomyopathy etc), one should be aware of multiple imprinting defects, especially PHP1B, in patients with BWS. We therefore advise that screening for PHP1B (either genetically or by monitoring calcium homeostasis during regular follow-up) should be considered in patients with BWS.

## Background

Although multiple imprinting defects have been found by genetic analysis in a subset of patients with BWS, very few patients have been described with both genetic and clinical signs and symptoms of multiple diseases caused by imprinting defects.

## Methods

Methylation analysis at KCNQ1OT1 and H19 was measured by methylation sensitive restriction digestion. Methylation analysis of the GNAS region was done by MLPA.

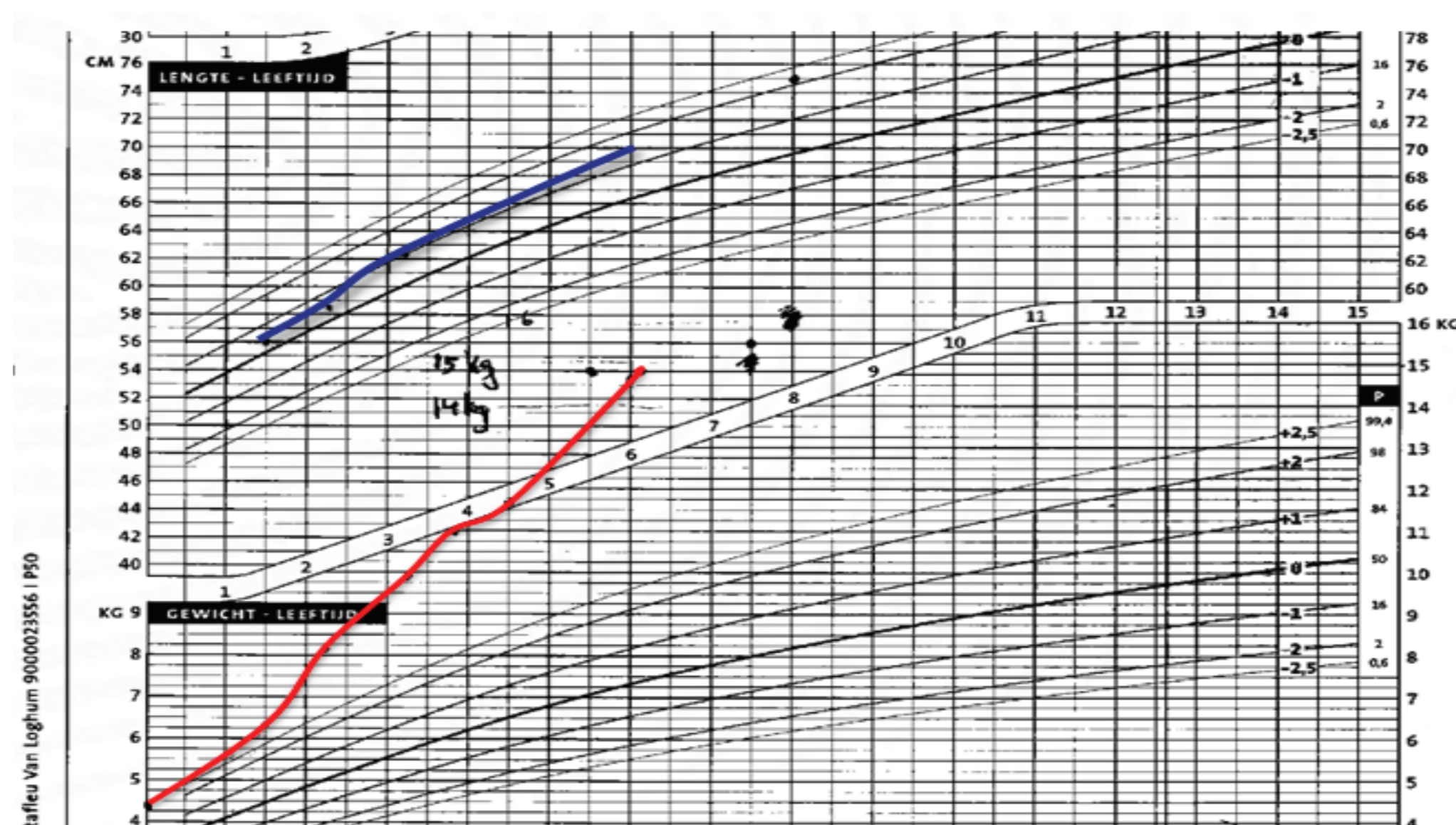


Figure 1. Growth chart

## Case report

**Girl 6 months old:** she presented with morbid obesity (BMI +7.5 SDS) (Figure 1) and a large umbilical hernia.

- Genetic analysis: hypomethylation of the KCNQ1OT1 gene (Figure 2), consistent with Beckwith-Wiedemann syndrome.
- Normal calcium homeostasis (Table 1).

**10 years old:** she presented with fatigue.

- Laboratory analyses: marked hypocalcaemia with signs of PTH resistance (high PTH, high phosphate, low urine phosphate, normal alkaline phosphatase). (Table 1)
- No signs of Albright hereditary osteodystrophy (AHO).
- PTH resistance in a patient without AHO-phenotype but with a known imprinting defect suggested PHP1B due to defective imprinting of the GNAS region (Table 2).
- Methylation analysis of the GNAS region (Figure 2) confirmed the diagnosis: hypomethylation (<20%) of the GNAS exon 1A, NESPAS and GNASXL loci and 100% methylation of NESP locus, consistent with the clinical diagnosis of PHP1B.

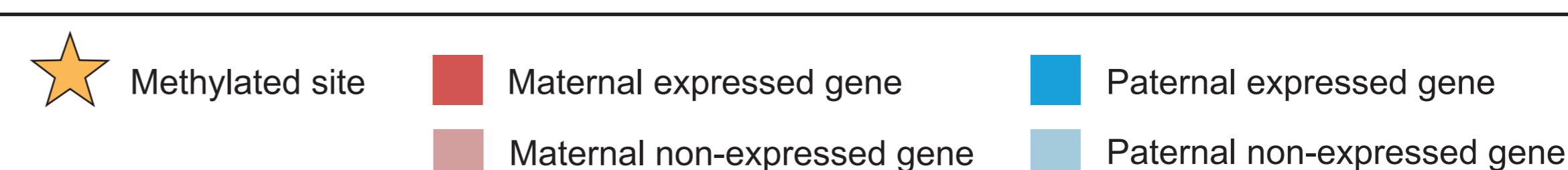
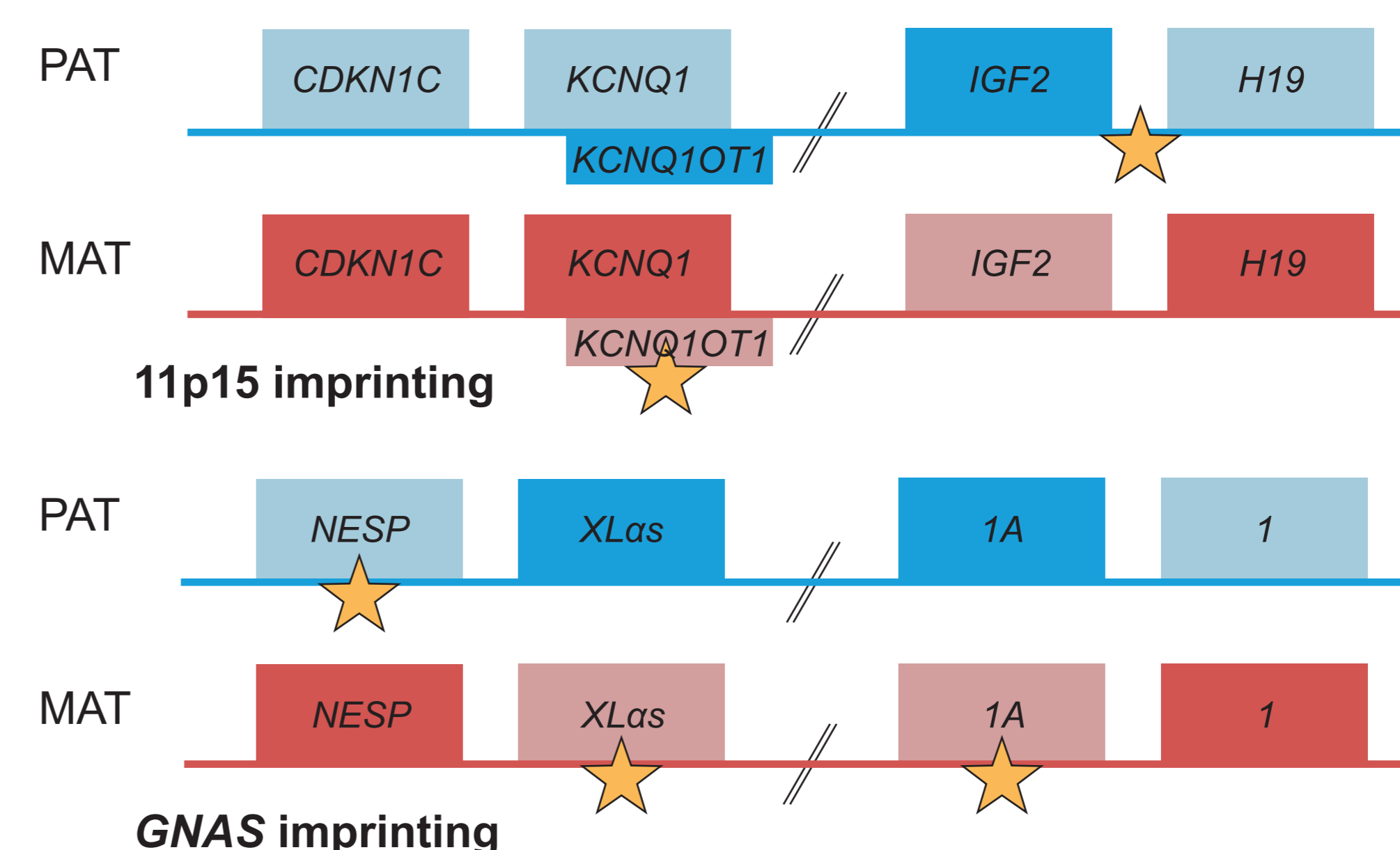


Figure 2. 11p15 imprinting and GNAS imprinting

	Ref.	Age 6 months	Age 10 years	Age 10 years after vitamin D treatment
Calcium (mmol/l)	2,20 - 2,65	2,57	1,90	1,92
Phosphate (mmol/l)	1,00 - 1,80	1,99	2,22	2,01
PTH (pmol/l)	1,9 - 11,3	5,6	50	67
25-OH Vit D (nmol/l)	50 - 185	-	27	60
Alkaline phosphatase (U/l)	0 - 500	-	272	232
Urine kreat (mmol/l)	5,0 - 15,0	-	15,4	7,0
Urine calcium (mmol/l)	2,5 - 7,5	-	< 0,5	< 0,5
Urine phosphate (mmol/l)	15 - 50	-	22	12

Table 1. Laboratory results

	AHO	GNAS gene defect	Hormone resistance
PHP1A	Yes	Maternal inactivating mutations	Multiple
PHP1B	No	Imprinting defects	PTH, TSH
PHP1C	Yes	Few inactivating mutations reported	Multiple
PPHP	Yes	Paternal inactivating mutations	No
POH	No	Paternal inactivating mutations	No

Table 2. Classification of pseudohypoparathyroidism

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## Abbreviations

MLPA, Multiplex Ligation-dependent Probe Amplification  
 AHO, Albright hereditary osteodystrophy;  
 PHP, pseudohypoparathyroidism;  
 PPHP, pseudopseudohypoparathyroidism;  
 POH, progressive osseous heteroplasia.