

PSEUDOHYPOPARATHYROIDISM TYPE Ib ASSOCIATED TO ASSISTED REPRODUCTIVE TECHNOLOGIES

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BACKGROUND

Pseudohypoparathyroidism type Ib (PHP-Ib) due to a maternal loss of GNAS exon A/B methylation leads to decreased expression of stimulatory G protein (G α) in specific tissues.

Evidence suggests an increased incidence of imprinting disorders in children conceived by Assisted Reproductive Technologies (ART).

Nevertheless, no associations between ART and PHP – Ib have been found to date.

CLINICAL CASE

7.4-years-old male with history of mild motor delay. Conceived by ART, born at 37 weeks appropriate for gestational age. At 4 yrs of age, an increased creatine kinase (CK) was detected.

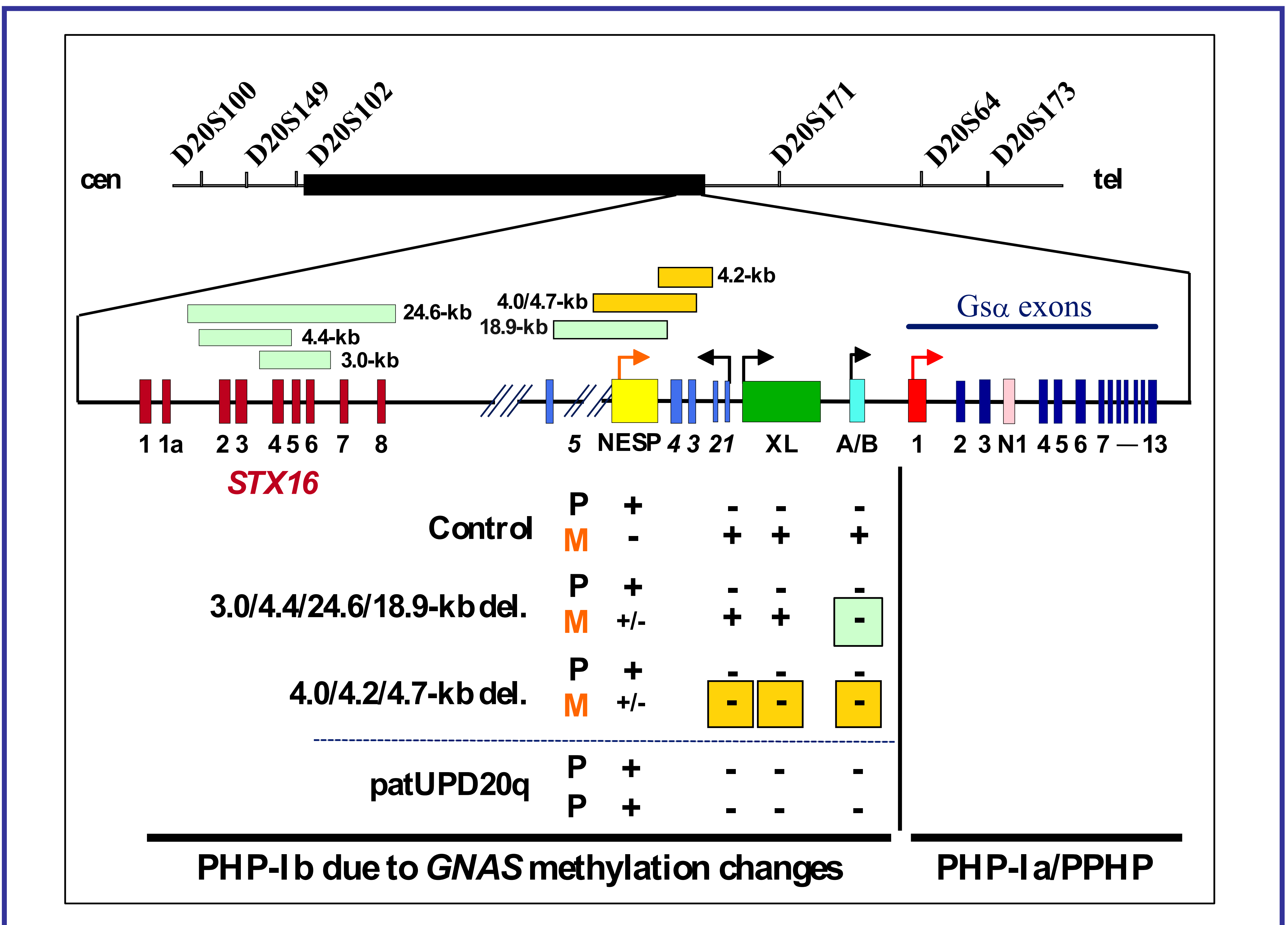
At 6 yrs after ruling out miopathy, an elevated PTH was detected with normal calcium, and alkaline phosphatase, normal high phosphorus and a low 25(OH) Vitamin D (Table). He was asymptomatic for Ca-P abnormalities, and diagnostic work-up excluded systemic, thyroid and adrenal diseases, inborn errors of metabolism, skeletal and chromosomal abnormalities.

Physical exam was unremarkable except for a narrow forehead, nasal bridge hypoplasia and micropenis.

Vitamin D supplementation increased 25(OH)D, but PTH remained high. Molecular studies confirmed an almost complete loss of methylation at GNAS exons A/B and AS, and a gain of methylation at exon NESP (Fig).

After 1 year of 0.5 ug QD of calcitriol treatment he remains asymptomatic, but mild developmental delay persists. Currently on learning supportive therapy. He presents biochemical improvement (Table). DEXA scan at age 8 years had normal areal and volumetric BMD. L2-L4 (+1.4, +2.0 SDS) and at the right and left hip (-1.1 SDS both).

DIAGNOSTIC WORK-UP & ANTHROPOMETRY	4-6 yrs	6.4 yrs (25OH-VitD Suppl)	7.6 yrs (1 year of 0.5 ug QD of calcitriol)
CK UI/L (NV<140)	200 – 278	154	133
PTH pg/ml (NV <60)	199	183	105
25 (OH) Vitamin D ng/ml	18.3	25.9	25.9
Calcium mg/dl	9.3	9.5	9.5
Phosphorus mg/dl	5.5	5.4	4.8
Alkaline Phosphatase UI/L	241	313	184
Birth Length SDS		-0.94	
Birth Weight SDS		-1.39	
Birth Head Circumference SDS		-1.83	
Current Height SDS		0.63	
Current BMI SDS		1.48	
Penile Length cm/SDS		3.2 / <-2	
Mid-parental Height SDS		-0.29	



CONCLUSIONS

We present a patient with PHP – Ib due to impaired methylation at GNAS exons A/B, AS and NESP most likely associated to ART.

References

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Lazaraviciute G, *et al.* A systematic review and meta-analysis of DNA methylation levels and imprinting disorders in children conceived by IVF/ICSI compared with children conceived spontaneously. *Hum Reprod Update.* 2014;20(6):840-52.