

Childhood obesity and normocalcaemia with a GNAS mutation also present in mother

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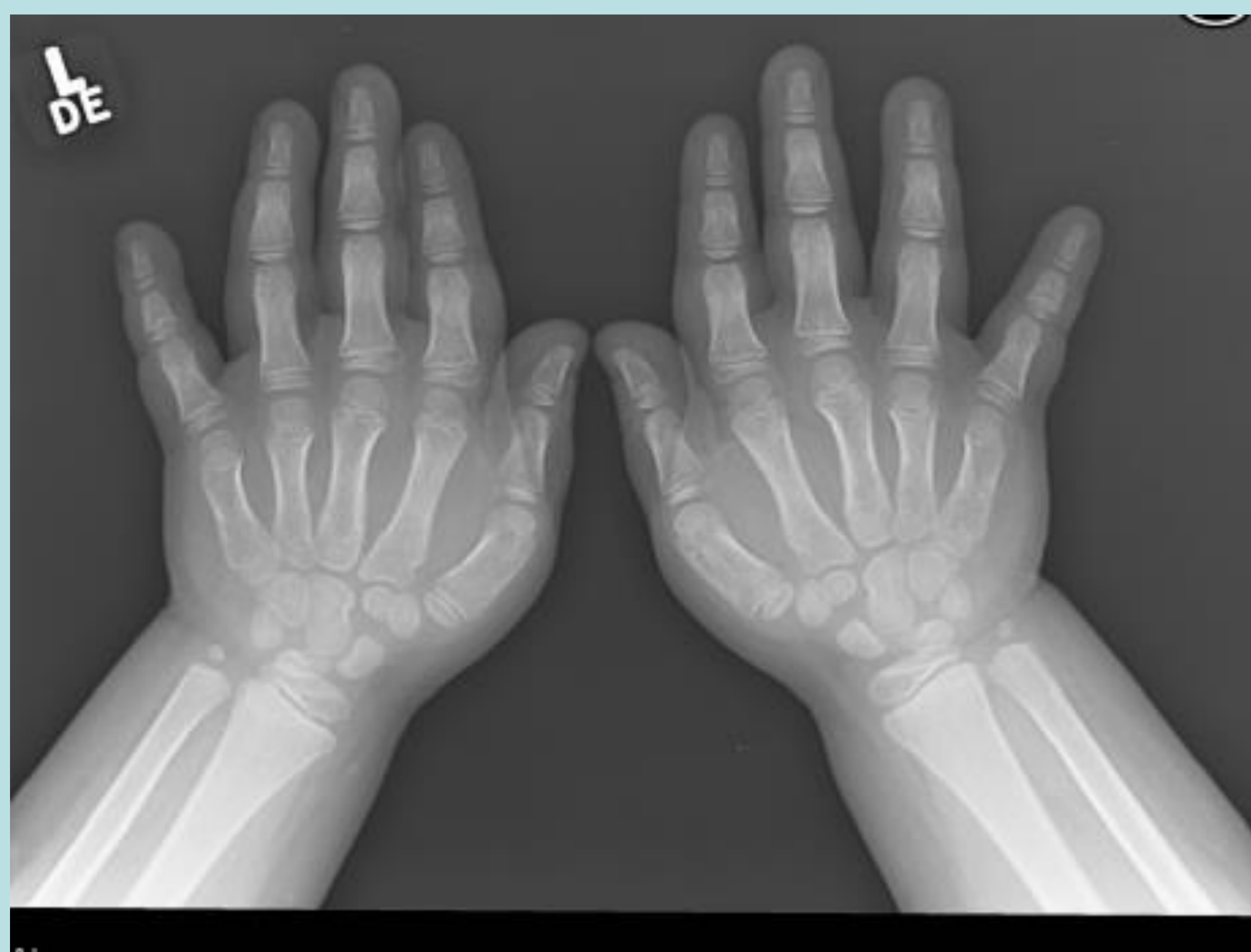
Mid Essex Hospital Services NHS Trust

Background: Assessment in childhood obesity includes looking for obesity syndromes. Dysmorphic features should guide investigations. When clinical signs are subtle, especially in early childhood, genetic investigations aid diagnosis. A case (S) of progressive childhood obesity is described. He was found to have a pathogenic GNAS mutation which was also present in his mother. Both mother and son had a similar phenotype and did not have hypocalcaemia or PTH resistance described in Pseudohypoparathyroidism type 1a (PHP1a).

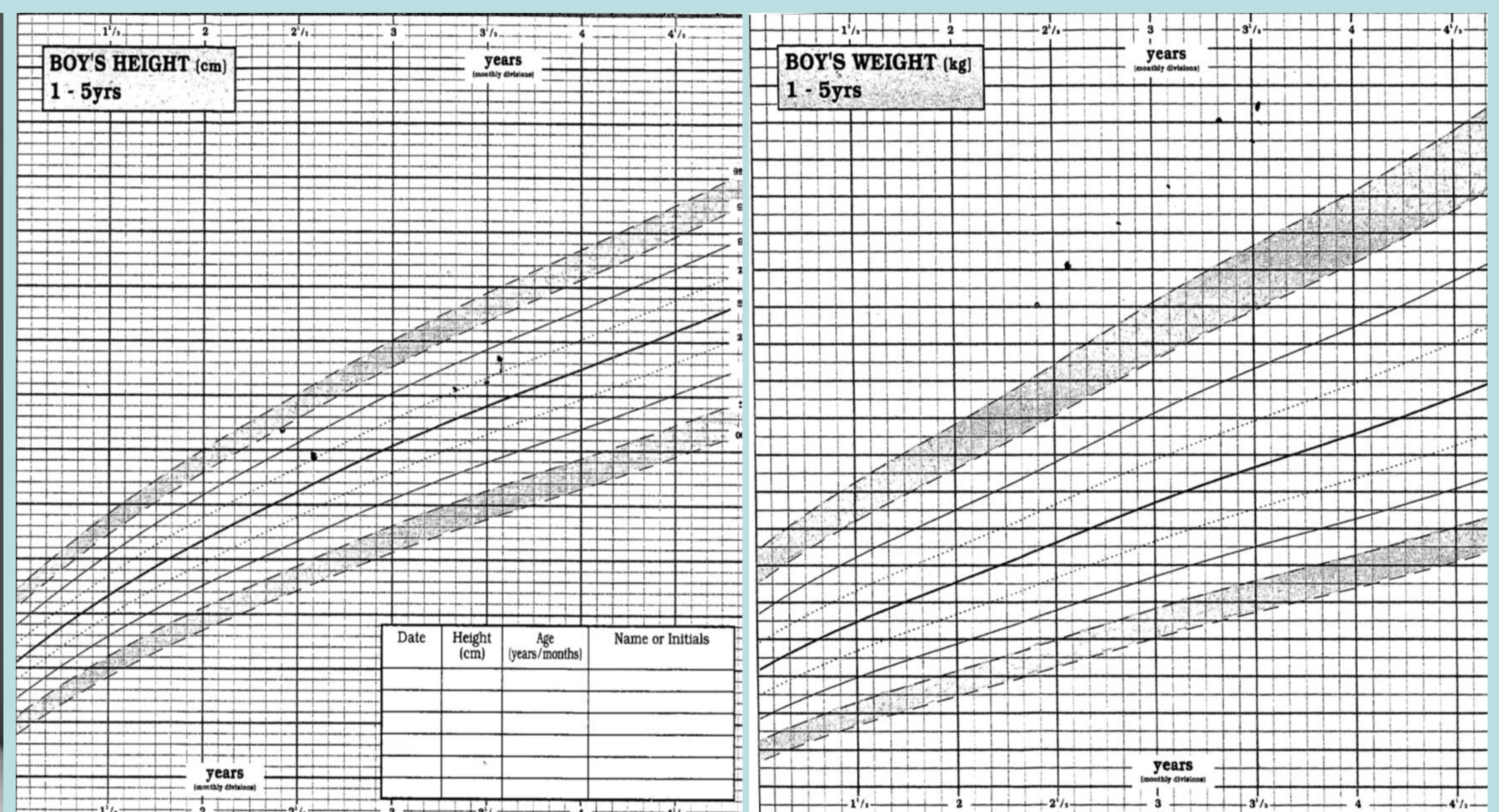
Case: S was referred at 6 years old for a growth assessment because of escalating weight from the age of 1 year. Birth weight at full term was normal at 3.66 kg. His height tracked along the 75th centile in his growth records and weight was above the 99.8th centile. S was well behaved and did not appear to have learning difficulties. On examination, S did not look overtly dysmorphic although he had a round face and mild rhizomelic limb shortening, brachyphalangy and no obvious shortening of the third or fourth metacarpals, no subcutaneous calcifications were palpable. His phenotype and digits were similar to his mother's. Mother's BMI was 35.5 kg/m².

Investigations: Due to his early onset of childhood obesity, he was enrolled into the Genetics of Obesity Study (GOOS). Skeletal survey, oral glucose tolerance test, metabolic screen, thyroid function, bone biochemistry and PTH levels were requested.

Results: The GOOS identified a heterozygous GNAS missense mutation. Because of this, extra investigations were requested. Skeletal survey showed generalised brachydactyly and brachymetacarpia, especially the fourth and fifth. Fasting glucose 4.5 mmol/L paired with Insulin 153 pmol/L, glucose at 120 min was 6.1 mmol/L. Calcium 2.36 mmol/L (2.12 – 2.55), PTH 6.1 pmol/L (1.2 – 9.3). Leptin concentration was normal for his percentage of body fat. Plasma insulin was raised but proinsulin and split proinsulin were normal. GNAS mutation analysis showed that he was heterozygous for R342Q, a missense mutation also present in his mother but not father and sister.



Hand X-rays



Growth chart

Conclusions: PHP1a is usually caused by maternally inherited G(s)alpha loss of function mutations in the GNAS gene. This condition includes Albright's Hereditary Osteodystrophy (AHO) and hypocalcaemia with PTH resistance. Maternal, but not paternal, G(s)alpha mutations lead to obesity, as in S. Renal tubules usually express the maternal GNAS gene, however bone biochemistry and PTH was normal in S, suggesting variable renal tubular expression of this imprinted gene. In S, mutation in exon 12 of GNAS appears to be associated with normocalcaemia and obesity. A previous case report of a child with normocalcaemia and pseudohypoparathyroidism 1a involved a missense mutation in exon 13. All other mutations described so far involving other exons from 1 to 11 appear to have varying degrees of hypocalcaemia and PTH resistance. Genetic screening in all children with significant early onset childhood obesity is an important investigation. We must not underestimate the role of imprinted genes in postnatal growth and metabolism.

References

- Mutational analysis of the GNAS1 exons encoding the stimulatory G protein in five patients with pseudohypoparathyroidism type 1a. Lim S et al. JPEM 2002;15(3):259-268.
- A pseudohypoparathyroidism type 1a patient with normocalcaemia. Tamada Y et al. Endocr J 2008;55(1):169-173.
- GNAS mutations in Pseudohypoparathyroidism type 1a and related disorders. Lemos MC, Thakker RV. Hum Mutat 2015;36(1):11-9.
- Recent advances in GNAS epigenetic research of pseudohypoparathyroidism. Izzì B et al. Curr Mol Med 2012;12(5):566-73
- The role of GNAS and other imprinted genes in the development of obesity. Weinstein LS et al. Int J Obes (Lon) 2010 Jan;34(1):6-17. doi: 10.1038/ijo.2009.222. Epub 2009 Oct 20.

The author has nothing to disclose

