Pseudohypoparathyroidism Type 1A Due to Novel *GNAS* Mutation

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I. Background: Pseudohypoparathyroidism (PHP) encompasses a group of rare disorders defined by target organ unresponsiveness to parathyroid hormone (PTH). Patients with PHP type 1A carry heterozygous mutations of the maternal *GNAS* gene that encodes the α-subunit of the G protein. This protein is coupled to the PTH receptor as well as to other heptahelical receptors : thyrotropin (TSH), growth hormone-releasing hormone (GHRH) and gonadotropins receptors.

II. Subject and methods:

- **The patient was born at 36 weeks gestation weighing 3535 grams after an uncomplicated pregnancy. Physical examination at birth was unremarkable except for umbilical hernia.**
- **At the 5th day of life, he developed hypothermia.**

Blood tests revealed:
TSH- 76 mIu/l (normal range:0.7-9.8),
FT4- 9.9 pmol/l (7-16) and FT3- 4 pmol/l (3.8-6).
Thyroid scan showed a normally located thyroid gland.
Levothyroxine treatment was initiated with normalization of TSH, FT4 and FT3 levels.

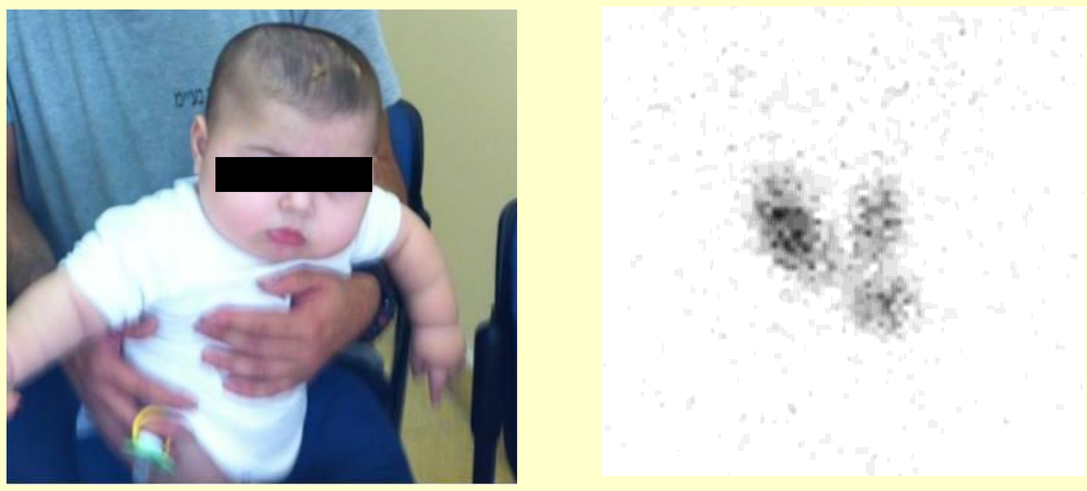
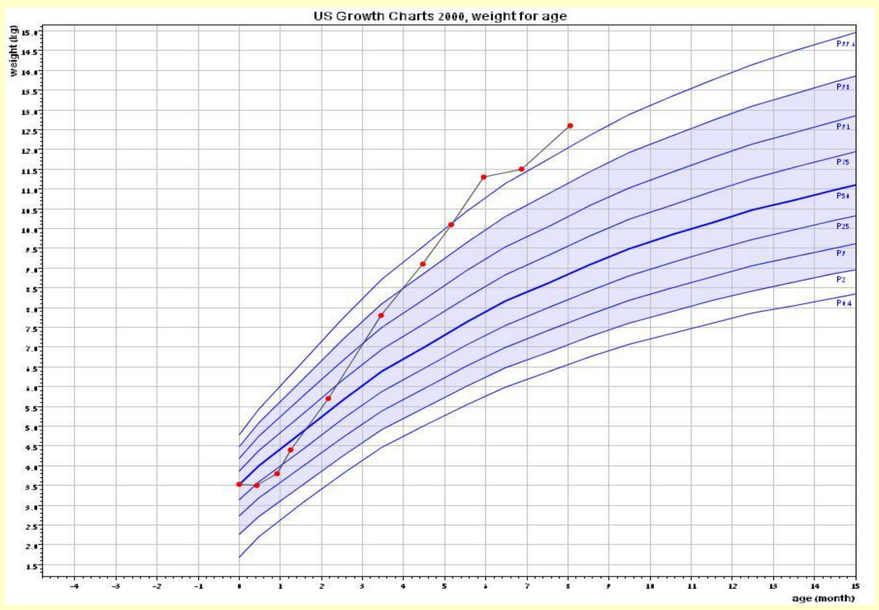


Figure 1: The patient and his thyroid scan

- **Excessive weight gain ensued and at 6 months he weighed 11.3kg (+3.3 SDS for his age).**



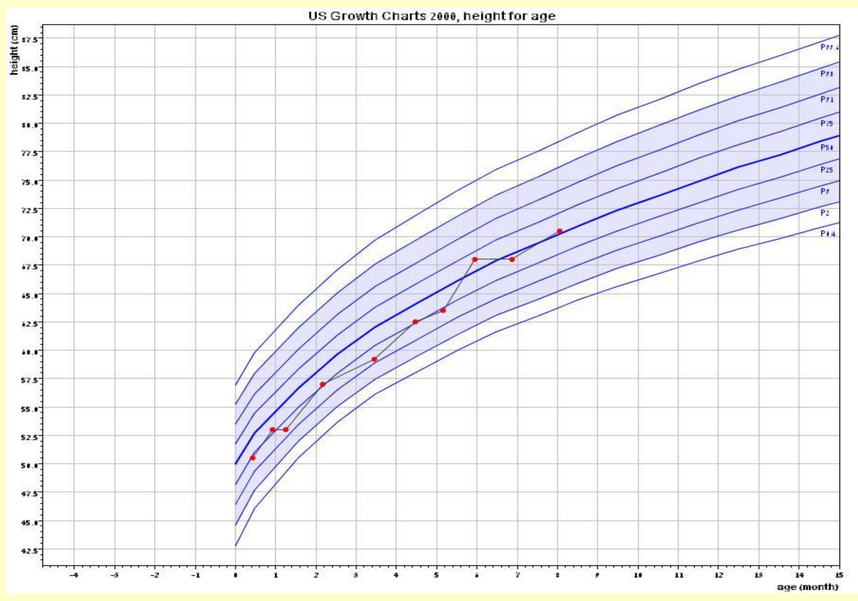


Figure 2: Weight and height growth charts

- **Workup: PTH-91.8, 129 and 211 pg/ml in sequential blood tests (nl=16-87), calcium-9.7 mg/dl, phosphorus 6.7 mg/dl, 25-hydroxy vitamin D-21.9 ng/ml (nl =20-100) calcium/creatinine ratio in the urine-0.02.**
Both parents had unremarkable physical examination and lab results.
- **DNA was extracted from whole blood and full sequencing of the coding regions of the *GNAS* gene was performed.**

III. Results: Sequence analysis revealed a novel heterozygous frameshift mutation with a premature stop codon in exon 7 (c.518_521delACTG). This mutation has not been previously reported and is predicted to be deleterious. Neither parent carried the mutation.

IV. Conclusion: This case presents a novel de-novo *GNAS* mutation. Physicians should consider the rare diagnosis of PHP among neonates with congenital hypothyroidism with normally located gland and marked obesity in the newborn period.