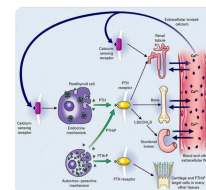


## A new mutation associated with pseudohypoparathyroidism? 2 case reports.

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### INTRODUCTION

- Pseudohypoparathyroidism is a metabolic disorder characterized by peripheral resistance to the action of parathyroid hormone (PTH) which can associate other hormonal disturbances. Their molecular basis is a defect in adenylyl cyclase Gs system encoded by the GNAS gene receptor.

### CASE REPORTS

- We describe the clinical case of 2 childbearing age women with thyroid dysfunction, hypocalcemia, hyperphosphatemia, and high levels of PTH.
- In both cases, mineral metabolism was normal in first-degree relatives.
- Both patients are asymptomatic and remain safe levels of calcium under treatment with calcium and vitamin D.

#### Clinical and analytical variables

	Case 1	Case 2
Sex/Country	Woman/Spain	Woman/Nepal
Age (years)	34	40
Diagnosis	Infertility (3 y), Microprolactinoma, Autoimmune primary hypothyroidism and obesity	Mild osteopenia, subclinical hypothyroidism and hospitalization for severe hypocalcemia and tetany.
Symptoms	Irregular menstrual cycles and fatigue	Asymptomatic under treatment (Calcium and vitamin D)
Weight (kg)	130	63
Height (cm)	155	154
Physical examination	Cervical acanthosis nigricans and round face	Brachydactyly of the 5th finger of hand
Calcium (mg/dl)	6.6	6.3
Phosphorous (mg/dl)	4.9	5.1
PTH (pg/ml)	244	547
Vitamin D (ng/ml)	15	37
GNAS gene mutation	No	No
Polymorphisms in heterozygosis	c.393C>T(p.Ile131Ile) c.1038+55T>C(IVS12 +155)	c.393C>T(p.Ile131Ile) c.586-42G>A (IVS7-42)

#### Different phenotypic and biochemical expressions of pseudohypoparathyroidism

Type	Heredity	Albright hereditary osteodystrophy	Ca/P	PTH	Hormone resistance	Gs mutation	cAMP (urine)	Phosphorus (urine)
Ia	Autosomal dominant	Yes	↑/↓	↑	Thyrotropin, glucagon, gonadotropins	GNAS1 mutation	No↓	No↓
Ib	Sporadic/autosomal dominant	No	↑/↓	↑	Occasional PTH renal and/or thyrotropin resistance	No GNAS1 mutation. Mutación 20q13.3 exón 1	No↓	No↓
Ic		Yes	↑/↓	↑	Yes	No	No↓	No↓
II	No Acquired vs intercurrent abnormalities?	No	↑/↓	↑	No	Unclassified	Yes (N)	No↓
PPHP	Autosomal dominant	Yes	N/N	N	No	GNAS1 mutation	Yes (N)	Yes↑

**Note:** Reference values: calcium 8.5-10.10 mg/dl, phosphorus 2.70-4.5 mg/dl, PTH 7-74 pg/ml and vitamin D > 30 ng/ml.

### Treatment

- Treatment with vitamin D or analogues is necessary to normalize serum calcium. Fixed preparations of calcium and vitamin D are not recommended. Treatment must get low-normal range of serum calcium.
- Use thiazides if there is significant hypercalciuria. In this cases, an ophthalmologic examination and renal ultrasound should be done to exclude cataracts and nephrolithiasis/nephrocalcinosis, respectively.
- Teriparatide or synthetic PTH 1-34 could be an option in patients with evidence or risk of nephrocalcinosis, because it normalizes serum calcium without increasing calciuria.

### CONCLUSION

- We describe two suspected cases of pseudohypoparathyroidism type 1a or 1c with negative genetic test for mutations in the GNAS gene but with a common polymorphism in heterozygosis.
- No GNAS gene mutations are detected in 30-40% of pseudohypoparathyroidism so many of their molecular mechanisms are not known.
- We think that polymorphism c.393C>T(p.Ile131Ile) could be a new mutation related to pseudohypoparathyroidism.