Refractory Hypocalcemia from Combined Autosomal Dominant Hypocalcemia Type 2 and Postsurgical Hypoparathyroidism

Journal:	*Journal of Bone and Mineral Research*
Manuscript ID	ASBMR-25090712.R2
Manuscript type:	Complex Clinical Challenges
Date Submitted by the Author:	n/a
Complete List of Authors:	Sonmez Ince, Melda ; University of Michigan, Division of Metabolism, Endocrinology & Diabetes Esfandiari, Nazanene H; University of Michigan, Division of Metabolism, Endocrinology & Diabetes Hannan, Fadil; University of Oxford, Nuffield Department of Women's & Reproductive Health Hussain, Mehboob A; University of Michigan, Division of Metabolism, Endocrinology & Diabetes; University of California Davis, Division of Endocrinology Giordano, Thomas; University of Michigan, Department of Internal Medicine, Division of Metabolism, Endocrinology and Diabetes; University of Michigan, Department of Pathology Haymart, Megan; University of Michigan, Metabolism, Endocrinology and Diabetes Thakker, Rajesh; University of Oxford, Oxford Centre for Diabetes, Endocrinology and Metabolism Clines, Gregory; University of Michigan, Division of Metabolism, Endocrinology & Diabetes; Ann Arbor Veterans Affairs Healthcare System, Medicine
Keywords:	PTH/Vit D/FGF23 < CELL/TISSUE SIGNALING - Endocrine Pathways, Other < DISORDERS OF CALCIUM/PHOSPHATE METABOLISM, Parathyroid-related disorders < DISORDERS OF CALCIUM/PHOSPHATE METABOLISM, Hormone replacement/receptor modulators < THERAPEUTICS, Other < CELL/TISSUE SIGNALING - Endocrine Pathways
Abstract:	A 49-year-old female with a history of chronic hypocalcemia, diagnosed twenty years earlier, had serum calcium concentrations that ranged between 6.4 and 8.5 mg/dL (nl, 8.6-10.3 mg/dL) with inappropriately low to low-normal parathyroid hormone (PTH) concentrations. She did not report symptoms of hypocalcemia such as paresthesias, muscle cramping, or tetany. More recently, a thyroid nodule was discovered, and the patient subsequently underwent total thyroidectomy for papillary thyroid cancer. Parathyroid autotransplantation was not performed since parathyroid glands were not identified during the surgery. After total thyroidectomy, the patient developed a more severe symptomatic, refractory hypocalcemia with undetectable PTH concentrations. Postoperative pathologic examination identified a single hypercellular

	parathyroid gland. Despite medical treatment including frequent and regular calcium gluconate infusions, serum calcium concentrations remained persistently low. A genetic evaluation identified a pathogenic GNA11 variant (c.178C>T, p.Arg60Cys), consistent with autosomal dominant hypocalcemia type 2 (ADH2). This case expands the understanding of ADH2 and raises important questions about optimal treatment strategies in patients with coexisting genetic and postsurgical hypoparathyroidism.

Title

Refractory Hypocalcemia from Combined Autosomal Dominant Hypocalcemia Type 2 and Postsurgical Hypoparathyroidism

Authors

Melda Sonmez Ince[1], Nazanene H. Esfandiari[1], Fadil M. Hannan[2], Mehboob A. Hussain[1,3], Thomas J. Giordano[1,4], Megan R. Haymart[1], Rajesh V. Thakker[5,6,7], and Gregory A. Clines[1,8]

[1]Division of Metabolism, Endocrinology & Diabetes, Department of Internal Medicine, University of Michigan, Ann Arbor, MI
[2]Nuffield Department of Women's & Reproductive Health, University of Oxford, Oxford, UK
[3]Division of Endocrinology, Department of Medicine, University of California, Irvine, Irvine, CA
[4]Department of Pathology, University of Michigan, Ann Arbor, MI
[5]Academic Endocrine Unit, University of Oxford, Oxford, UK
[6]National Institute for Health Research Oxford Biomedical Research Centre, Oxford, UK
[7]Centre for Endocrinology, William Harvey Research Institute, Barts and the London School of Medicine, Queen Mary University of London, London, UK
[8]Ann Arbor Veterans Affairs Healthcare System, Ann Arbor, Michigan

Corresponding Author:

Gregory A. Clines, M.D., Ph.D.
Associate Professor of Internal Medicine
Division of Metabolism, Endocrinology & Diabetes
Department of Internal Medicine
University of Michigan
Endocrinology Section, Ann Arbor VA Healthcare System
2215 Fuller Road, Research 151
Ann Arbor, Michigan 48105-2399
clines@med.umich.edu

Data Availability Statement:

Datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Conflict of Interest Statement:

None declared

Key Words:

hypoparathyroidism, autosomal dominant hypocalcemia type 2 (ADH2), *GNA11* mutation, postsurgical hypoparathyroidism, parathyroid hormone (PTH) therapies

Vignette

A 49-year-old female with a history of chronic hypocalcemia, diagnosed twenty years earlier, had serum calcium concentrations that ranged between 6.4 and 8.5 mg/dL (nl, 8.6-10.3 mg/dL) with inappropriately low to low-normal parathyroid hormone (PTH) concentrations. She did not report symptoms of hypocalcemia such as paresthesias, muscle cramping, or tetany. More recently, a thyroid nodule was discovered, and the patient subsequently underwent total thyroidectomy for papillary thyroid cancer. Parathyroid autotransplantation was not performed since parathyroid glands were not identified during the surgery. After total thyroidectomy, the patient developed a more severe symptomatic, refractory hypocalcemia with undetectable PTH concentrations. Postoperative pathologic examination identified a single hypercellular parathyroid gland. Despite medical treatment, including frequent and regular calcium gluconate infusions, serum calcium concentrations remained persistently low. A genetic evaluation identified a pathogenic *GNA11* variant (c.178C>T, p.Arg60Cys), consistent with autosomal dominant hypocalcemia type 2 (ADH2)**.** This case expands the understanding of ADH2 and raises important questions about optimal treatment strategies in patients with coexisting genetic and postsurgical hypoparathyroidism.

Case Description

A 49-year-old female had a 20-year chronic documented hypocalcemia with a corrected serum calcium of 6.4-8.5 mg/dL (nl, 8.6-10.3 mg/dL), a PTH of 9-21 pg/mL (nl, 10-65 pg/mL), and a normal 24-hour urine calcium concentration (**Table**). Because of the lack of hypocalcemia symptoms and the apparent absence of family members with hypocalcemia, the patient's primary physician did not pursue a thorough endocrinologic evaluation.

The patient was known to have thyroid nodules, as a neck ultrasonography performed at 39 years of age reported bilateral thyroid nodules. The patient reported no known history of significant radiation exposure. At 49 years of age, the patient's primary care physician palpated a right thyroid nodule, which prompted a neck ultrasound, reporting three Thyroid Imaging Reporting and Data System (TI-RADS) class 4 nodules: Right inferior lobe 1.7 x 1.3 x 1.6 cm nodule, left mid-lobe 1.5 x 0.6 x 1.1 cm nodule, and a right inferior isthmus 0.9 x 0.9 x 1.1 cm nodule. The patient underwent FNA evaluation of the right inferior isthmus nodule, with pathological examination reporting papillary thyroid cancer (PTC). Given the diagnosis of PTC and the bilateral nature of the TI-RADS 4 nodules, the patient elected for a total thyroidectomy. The decision for a total thyroidectomy was aligned with the 2015 American Thyroid Association guidelines for the management of PTC.

She underwent a total thyroidectomy without parathyroid autotransplantation since parathyroid glands were not identified during the intraoperative histologic survey. A surgical pathologic examination reported an isthmus 1.3 x 1.0 x 0.5 cm follicular-variant PTC and a right 0.4 cm secondary microcarcinoma. Despite an extensive histologic evaluation of the resected thyroid gland, only a single parathyroid gland was identified (**Figure 1**). The gland was characterized as hypercellular with minimal stromal adipose and increased numbers of chief and oxyphil cells, as is typically seen in hypercellular parathyroids in a variety of clinical contexts. Due to the patient's low-risk thyroid cancer (TNM Stage: T1bNxMx), radioactive iodine ablation was not performed. The patient was prescribed levothyroxine 125 mcg daily.

After the total thyroidectomy, the patient's serum calcium values were even lower (5.6-6.7 mg/dL) (**Figure 2**), requiring multiple emergency department visits and IV calcium gluconate infusions due to hypocalcemic symptoms, mainly hand cramping and paresthesias. The patient was diagnosed with post-surgical hypoparathyroidism (PSHP) with a persistently undetectable PTH. The only other abnormal laboratory value was an elevated phosphate concentration of 8.9

mg/dL (nl, 2.7-4.6 mg/dL). The following laboratory values were normal: magnesium of 1.7 mg/dL (nl, 1.6-2.6 mg/dL), alkaline phosphatase (ALP) 80 IU/L (nl, 40-116 IU/L), and glomerular filtration rate (GFR) 75 mL/min/1.73 m^2 (nl, >59 mL/min/1.73m^2).

Clinical Problem

Postsurgical hypoparathyroidism (PSHP) is a clinically challenging condition to manage, with patients often requiring multiple emergency department visits due to hypocalcemia. Even with treatment strategies that successfully bring serum calcium concentrations to near normal, patients are at risk for nephrolithiasis, skeletal fractures, cataracts, and neuropsychiatric symptoms that include cognitive dysfunction, anxiety, depression, and fatigue. Acute declines in serum calcium concentrations or more chronic severe hypocalcemia can result in acral paresthesias, muscle cramping, tetany, seizures, cardiac arrhythmias, basal ganglia calcifications, and death. It is crucial for patients to receive appropriate treatment, which can help prevent many of these complications.

Differential Diagnosis and Investigations

The patient described here experienced a complication of a total thyroidectomy—postsurgical hypoparathyroidism. The surgery occurred four years previously and so there is little chance of any substantial PTH secretion recovery. Notably, a chronic, asymptomatic hypocalcemia had existed for at least the past twenty years. Non-surgical causes of hypocalcemia are rarer. Like many organs, the parathyroid glands can undergo infiltrative transformation due to copper deposition in Wilson disease and iron deposition in hemochromatosis. A laboratory evaluation for Wilson disease and hemochromatosis was completed with normal values: serum copper 1.5 µg/mL (nl, 0.7–1.6 µg/mL), serum ceruloplasmin 33 mg/dL (nl, 18–42 mg/dL), serum iron 63 µg/dL (nl, 33–150 µg/dL), total iron-binding capacity 291 µg/dL (nl, 220–440 µg/dL), transferrin saturation 22% (nl, 20–50%), and serum ferritin 74.3 ng/mL (nl, 7.0–271.0 ng/mL). Metastatic infiltration of cancer cells is another cause of infiltrative hypoparathyroidism. Still, other than early-stage thyroid cancer, there was no suspicion that the patient had another cancer, and at least a twenty-year history of chronic hypocalcemia would not be consistent with a metastatic disease.

After postsurgical complications, genetic syndromes are the next most common cause of hypoparathyroidism. Mutations in the *AIRE* gene cause autoimmune polyendocrine syndrome type 1, characterized by hypoparathyroidism, chronic mucocutaneous candidiasis, primary adrenal insufficiency, and other disorders. The patient had no history of candidiasis, and an evaluation for adrenal insufficiency was normal. Mutations in *CASR* are another cause of hypoparathyroidism. The calcium-sensing receptor (CaSR), encoded by *CASR* and expressed in tissues including the parathyroid gland and kidney, detects elevated plasma ionized calcium and responds by suppressing parathyroid hormone secretion and reducing renal calcium reabsorption. Gain-of-function mutations in *CASR* are the cause of autosomal dominant hypocalcemia type 1 (ADH1) [1]. This defect leads to an increased sensitivity of parathyroid and renal cells to extracellular calcium, resulting in hypocalcemia and hypercalciuria [2]. Extracellular calcium-sensing by CaSR transmits signals to the G protein subunit alpha-11 protein (Gα11), encoded by *GNA11*, and thus gain-of-function mutations in this gene nearly phenocopy ADH1, resulting in autosomal dominant hypocalcemia type 2 (ADH2).

Due to the chronic hypocalcemia before thyroidectomy and the suspicion that the patient had a genetic etiology contributing to the hypocalcemia, she was referred to an academic medical center genetics clinic. Genetic testing identified a pathogenic heterozygous variant of

GNA11 (c.178C>T, p.Arg60Cys), consistent with ADH2 [3]. This gain-of-function mutation increases the sensitivity of the calcium-sensing receptor (CaSR) to extracellular ionized calcium, leading to an inappropriate decrease in PTH secretion and reduced renal tubular reabsorption of calcium across a range of plasma calcium concentrations, compared to individuals without the mutation. Mutations of other genes that cause hypocalcemia, including *AIRE*, *AP2S1*, *CASR*, *GCM2*, and *PTH,* were not identified.

Diagnosis

Autosomal dominant hypocalcemia type 2 and postsurgical hypoparathyroidism

Treatment and Progression

Due to persistently low serum calcium concentrations and associated symptoms, the patient was prescribed intravenous calcium gluconate 2-4 gram infusions three times weekly, necessitating the placement of an implanted intravenous port to accommodate the frequency of the infusions. She was also prescribed oral calcium carbonate, calcitriol, cholecalciferol, and magnesium supplements. Despite escalation of up to eight grams of elemental calcium supplements and 12 mcg of calcitriol daily, with a goal serum calcium of at least 7.5 mg/dL, attempts to wean her off infusions were unsuccessful.

A gastrointestinal malabsorption syndrome was considered; however, IgG and IgA antibodies to transglutaminase were undetectable, supporting the absence of celiac disease. The patient also has a normal body mass index, and without a history of chronic diarrhea or pancreatic insufficiency. Provocative testing was performed with supervised administration of 4 mcg of calcitriol, resulting in an increase from a baseline 1,25-dihydroxyvitamin D of 10 pg/mL to 35 pg/mL two hours after dose administration, with expected peak serum concentrations three to six hours after oral administration. This result argued against severely impaired absorption of the medication.

The addition of chlorthalidone 12.5 mg daily, to increase renal calcium reabsorption, had little benefit. Serum phosphorus concentrations were also elevated; therefore, sevelamer 800 mg three times daily was added to the treatment regimen. Paricalcitol 1 mcg IV was also added to her thrice-weekly infusions. Despite these interventions, the patient's serum calcium values remained below 7.0 mg/dL.

The patient was then prescribed teriparatide with dosing up to 20 mcg twice daily and subsequently transitioned to continuous subcutaneous delivery using an insulin pump, receiving 40 mcg of teriparatide daily. The patient's serum calcium continued to be low. She was then transitioned to palopegteriparatide, with dosing escalations to 30 mcg daily. Despite this therapy, the patient's hypocalcemia continued to require regular intravenous calcium gluconate infusions. The patient was offered to increase palopegteriparatide injections to greater than 30 mcg daily. However, the patient declined the dose escalation since this would require an increase from one to two injections daily. Due to the excessive pill burden, the patient was ultimately successful taking calcium carbonate 1500 mg (elemental calcium) four times daily and calcitriol 2 mcg twice daily. Serum calcium concentrations remained 6.2-6.9 mg/dL. She reported continued, but improved, hypocalcemia symptoms, mainly muscle cramping, occurring several times weekly, and occurrences of acral paresthesias occurring monthly. We interpret the gradual attenuation of these symptoms as adaptive changes to neuronal membrane excitability in response to chronic hypocalcemia.

Renal sonography performed two years after and an abdominal CT performed three years after surgery identified neither nephrolithiasis nor nephrocalcinosis. Random urine calcium to

creatine ratio was 0.109 mg/mg (nl, <0.20 mg/mg), indicating the absence of hypercalciuria. Hypercalciuria is often absent in ADH2, but even combined with postsurgical hypoparathyroidism, the urine calcium in this patient remained normal. Left globus pallidus calcification was visible on a brain computed tomography imaging; however, the patient has no documented neurological or psychiatric diagnosis. The patient had not undergone previous brain imaging, and so it is unclear whether the calcifications existed before the surgery or were a consequence of more severe hypocalcemia after surgery. Furthermore, the patient's daughter was also diagnosed with ADH2 and carried the same mutation as the patient. She had mildly low calcium levels, reporting occasional muscle cramping only with exercise.

The patient continues to be recurrence-free from papillary thyroid cancer, with undetectable serum thyroglobulin concentrations. Thus, target serum TSH concentrations have been 0.5-2.0 mIU/L.

Discussion

Hypoparathyroidism is uncommon, with a prevalence estimated to be 37 out of 100,000 persons in the United States [4]. Neck surgery is the most frequent cause of hypoparathyroidism and is a complication in 1-3% of total thyroidectomies [1]. The availability of experienced high-volume surgeons decreases the risk of hypoparathyroidism. Although PSHP was a complication after total thyroidectomy with undetectable serum PTH, the patient was also diagnosed with ADH2. This is a rare disorder; the prevalence is unknown, and published reports are limited [3,5]. Mannstadt et al. described a family with the same mutation as described here, causing hypoparathyroidism, with affected family members having low calcium levels accompanied by low or inappropriately normal PTH levels, as well as high-normal or high phosphate levels [3]. Although ADH1 and ADH2 have similar characteristics, patients with ADH2 exhibit less urine calcium excretion than those with ADH1 and may be at a lower risk for kidney stones.

The physiology of patients with ADH2 is distinct and presents with unique challenges. Even with calcium and calcitriol treatment, patients with the gain-of-function *GNA11* mutations have persistent hyperactivation of the CaSR–Gα11 pathway, suppressing PTH secretion and further promoting renal calcium wasting. In the case of the patient reported here, the complete removal of PTH further exacerbates hypocalcemia by reducing PTH-dependent stimulation of renal 1α-hydroxylase, leading to decreased production of 1,25-dihydroxyvitamin D in proximal tubules and, consequently, diminished intestinal absorption of calcium and phosphate. Furthermore, parathyroidectomy eliminates residual PTH reserve in ADH2, leading to increased renal calcium losses and worsening hypocalcemia.

Conventional management of hypoparathyroidism involves calcium and active vitamin D supplements to maintain a serum calcium concentration within the lower range of normal. Thiazide diuretics increase renal calcium reabsorption and can thus be used as an additive agent to control hypercalciuria, especially in individuals at risk for nephrocalcinosis and kidney stone formation. In the event of hyperphosphatemia that cannot be adequately managed with adjustments to calcitriol and calcium supplements, phosphate binders such as sevelamer can also be used.

PTH replacement therapy can be considered for patients with hypoparathyroidism who are poorly controlled with conventional treatment [1]. In one study, recombinant human (rh) PTH (1-84) was compared to placebo in a study of 134 subjects, over 24 weeks in the REPLACE study. Subjects with genetic disorders comprised only 2% in each group, with activating mutations in the *CASR* gene or impaired responsiveness to PTH excluded from the study. Compared to only 2% of those receiving a placebo, 53% of those receiving rhPTH(1-84) achieved the target of normal serum calcium [6]. Endpoints included maintenance of blood calcium levels and reduction of the starting oral calcium dose or active vitamin by at least 50% [6]. Although the results of this

study were promising, rhPTH (1-84) became unavailable for standard prescribing in the U.S. in 2019. Continuous PTH has also been studied, with Winer et al. reporting that continuous PTH delivery in patients with postsurgical hypoparathyroidism, using an insulin pump, compared to a twice-daily PTH 1-34 injection regimen, resulted in 65% less overall daily PTH 1-34 required to maintain normal calcium levels [7]. Moreover, Sastre et al. investigated continuous PTH delivery in a series of patients with ADH1 presenting with hypocalcemic seizures. The treatment resulted in an increase in mean serum adjusted calcium by 0.30 mmol/L (95% CI, 0.12–0.48) and a reduction in mean serum phosphate by 0.92 mmol/L (95% CI, 0.69–1.14). Notably, seizure frequency decreased, and no patient required ongoing antiepileptic drugs [8].

Palopegteriparatide, a long-acting PTH 1-34 preparation, was studied in a double-blind, placebo-controlled, 26-week phase 3 clinical trial in subjects with hypoparathyroidism. In this study, subjects with genetic disorders were included, with 3% in the treatment group and none in the placebo group with an identified genetic mutation. However, the nature of the genetic defect was not specified. The primary composite endpoint was independence from conventional therapy (requiring no active vitamin D and less than 600 mg of calcium per day), no increase in study drug over the preceding four weeks, and normal albumin-adjusted serum calcium levels. At week 26, 79% of those who received palopegteriparatide, compared to 5% of those who received the placebo, achieved the primary composite effectiveness goal [9].

The calcilytic agent encaleret that targets CASR was reported in a phase 2b clinical trial to increase serum calcium concentrations in subjects with ADH1 [10] and is currently being evaluated in a phase 3 trial. Calcilytics increase the CaSR calcium-sensing threshold, compensating for the lower calcium-sensing threshold of ADH1. Increasing the threshold for calcium-sensing would also be expected to partially compensate for *GNA11*-activating mutations. Such an effect of calcilytic medications has been reported in an ADH2 mouse model [11] but has not yet been reported in human studies. It is doubtful that a calcilytic agent would confer significant benefit in the patient reported here, as these medications primarily target the parathyroid glands, which are absent in this patient. Alterations in renal calcium-sensing with calcilytics would also be expected to increase renal calcium reabsorption. However, significant hypercalciuria due to reduced renal calcium reabsorption is often not a complication in patients with ADH2, including the patient reported here, who did not have hypercalciuria, even before the thyroidectomy and the inadvertent total parathyroidectomy.

Unanswered Questions

The *GNA11* mutation carried by the patient activates Gα11 signaling, thereby not only raising the threshold for hypocalcemia-induced PTH secretion but also potentially playing a role in the parathyroid glands' embryonic development, as evidenced by the identification of a single, histologically hypercellular parathyroid gland embedded within the thyroid tissue. The mechanism by which *GNA11* potentially regulates parathyroid gland embryonic development is unclear. It is also possible that since no additional parathyroid glands were identified on the pathology report, the possibility of damage to or inadvertent removal of other parathyroid glands cannot be excluded.

It is essential to note that Gα11 is ubiquitously expressed and participates in signaling pathways beyond the CaSR signaling, including the PTH receptor-dependent signaling. PTH binding to the PTH receptor, a G-protein-coupled receptor, activates a cellular signaling cascade with engagement of not only Gαs but also Gα11, Gα12/13, Gαi, and β-arrestin [12]. The refractory nature of the patient to PTH analog therapy may suggest that the *GNA11*-activating mutations also reduce PTH sensitivity in target organs, such as bone and kidney, and thus render PTH analogs, such as palopegteriparatide, less effective. Another explanation of the patient's treatment refractoriness is medication non-compliance, which is certainly within the

spectrum of neuropsychiatric manifestations of chronic hypocalcemia. However, the patient continuously assured the treating team of her adherence to the recommended treatment regimen.

Conclusions and Future Directions

ADH2, due to gain-of-function mutations of *GNA11*, which encodes Gα11, causes lifelong hypocalcemia that is often asymptomatic and undiagnosed. We report here the first documented case of combined ADH2 and PSHP, and the first report of parathyroid gland histologic characteristics in ADH2. Clinicians should use caution in patients with undiagnosed calcium or PTH abnormalities before undergoing neck surgeries and consider genetic testing in cases of chronic hypocalcemia. This case highlights that patients with ADH2 require caution with procedures that may disrupt parathyroid gland function. Furthermore, the refractory nature of this patient's hypocalcemia may suggest that *GNA11* mutations in the kidney and skeleton reduce the effectiveness of standard hypocalcemia treatments. The findings from this unusual case suggest that Gα11 may play a role in calcium homeostasis beyond its interaction with the CaSR, indicating the need for further research to understand how *GNA11* mutations affect calcium regulation.

Key Points

- ADH2, due to gain-of-function mutations of *GNA11*, causes lifelong hypocalcemia that is often asymptomatic and undiagnosed.
- We report here the first documented case of combined ADH2 and PSHP.
- This case underscores the need for caution in patients with ADH2 undergoing procedures that may affect parathyroid gland function. Patients with complex or dual endocrinopathies, such as having both a thyroid nodule and hypocalcemia requiring surgery, should always have the surgery performed by a skilled, high-volume neck surgeon, with consideration of lobectomy rather than total thyroidectomy.
- The refractory nature of this patient's hypocalcemia may suggest that *GNA11* mutations in the kidney and skeleton reduce the effectiveness of standard hypocalcemia treatments.

References

1. Bilezikian, J. P. Hypoparathyroidism. *J Clin Endocrinol Metab* 105, 1722–1736 (2020).
2. Pearce, S. H. *et al.* A familial syndrome of hypocalcemia with hypercalciuria due to mutations in the calcium-sensing receptor. *N Engl J Med* 335, 1115–1122 (1996).
3. Mannstadt, M. *et al.* Germline Mutations Affecting Gα11 in Hypoparathyroidism. *N Engl J Med* 368, 2532–2534 (2013).
4. Clarke, B. L. *et al.* Epidemiology and Diagnosis of Hypoparathyroidism. *J Clin Endocrinol Metab* 101, 2284–2299 (2016).
5. Li, D. *et al.* Autosomal dominant hypoparathyroidism caused by germline mutation in GNA11: phenotypic and molecular characterization. *J Clin Endocrinol Metab* 99, E1774-1783 (2014).
6. Mannstadt, M. *et al.* Efficacy and safety of recombinant human parathyroid hormone (1-84) in hypoparathyroidism (REPLACE): a double-blind, placebo-controlled, randomised, phase 3 study. *Lancet Diabetes Endocrinol* 1, 275–283 (2013).
7. Winer, K. K. *et al.* Synthetic human parathyroid hormone 1-34 replacement therapy: a randomized crossover trial comparing pump versus injections in the treatment of chronic hypoparathyroidism. *J Clin Endocrinol Metab* 97, 391–399 (2012).
8. Sastre, A. *et al.* PTH infusion ameliorates seizures in autosomal dominant hypocalcemia type 1. *N Engl J Med* 385, 189–191 (2021).
9. Khan, A. A. *et al.* Efficacy and Safety of Parathyroid Hormone Replacement With TransCon PTH in Hypoparathyroidism: 26-Week Results From the Phase 3 PaTHway Trial. *J Bone Miner Res* 38, 14–25 (2023).
10. Gafni, RI. et al. Efficacy and safety of encaleret in autosomal dominant hypocalcemia type 1. *N Engl J Med* 389, 1245-1247 (2023).
11. Roszko, KL. et al. Knockin mouse with mutant $G\alpha_{11}$ mimics human inherited hypocalcemia and is rescued by pharmacologic inhibitors. *JCI Insight* 2, e91079 (2017).
12. Bastepe, M., Turan, S. & He, Q. Heterotrimeric G proteins in the control of parathyroid hormone actions. *J Mol Endocrinol* 58, R203–R224 (2017).

Figure Legends

Figure 1: (A) Histopathological hematoxylin and eosin (H&E; 4x magnification) examination of hypercellular parathyroid gland (arrow marks parathyroid gland) surrounded by thyroid follicular epithelium. (B) Magnified view revealing hypercellular parathyroid gland (H&E, 200x magnification). Red arrows: chief cells; yellow arrows: oxyphil cells.

Figure 2: Serum calcium trend over time before and after the surgery

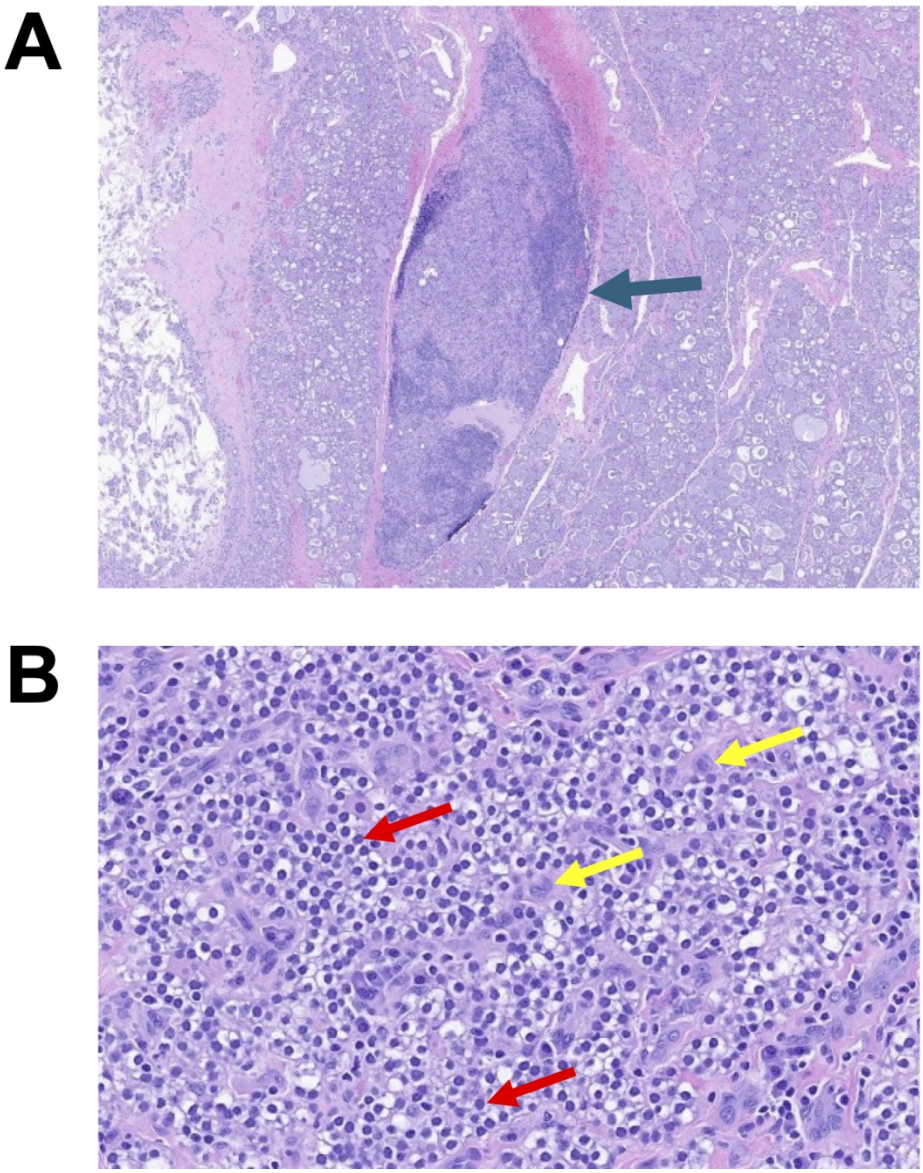

Figure 1: (A) Histopathological hematoxylin and eosin (H&E; 4x magnification) examination of hypercellular parathyroid gland (arrow marks parathyroid gland) surrounded by thyroid follicular epithelium. (B) Magnified view revealing hypercellular parathyroid gland (H&E, 200x magnification). Red arrows: chief cells; yellow arrows: oxyphil cells.

505x627mm (72 x 72 DPI)

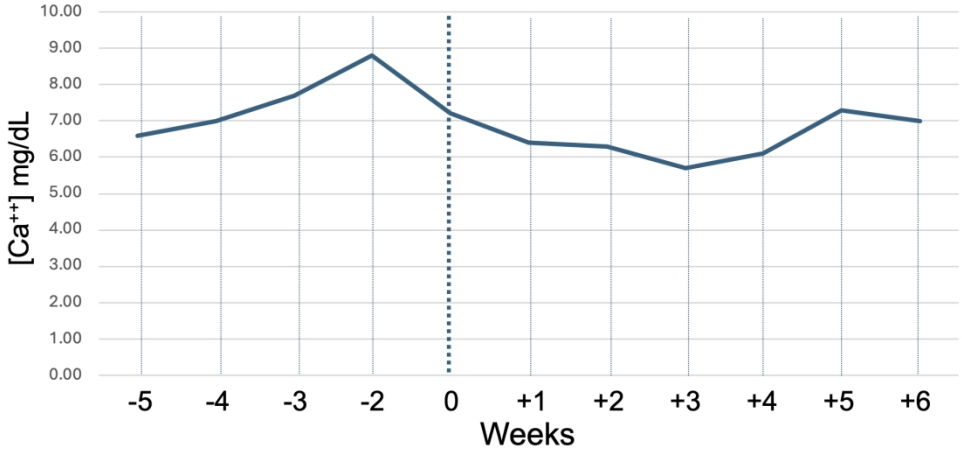

Figure 2: Serum calcium trend over time before and after the surgery

749x383mm (72 x 72 DPI)

Table

	-9 yr	-6 yr	-5 m	-1 m	-1 w	+2 w	+2 m	+ 6 m	+12 m	+24 m
Calcium (mg/dL) (nl, 8.6-10.3)	**7.7**	**8.5**	**7.0**	**6.6**	**8.0**	**6.6**	**7.3**	**6.0**	**6.4**	**6.8**
Albumin (g/dL) (nl, 3.5-4.9)	4.3	4.0	4.0			4.3	4.7			
Corrected calcium (mg/dL)	**7.5**	**8.5**	**7.0**			**6.4**	**6.7**			
PTH (pg/mL) (nl, 10-65)				20.1	**9**	**<1**	**<6**			
Cr (mg/dL) (nl, 0.50-1.00)	0.77	0.80	0.92	0.88	0.99	0.93	0.97	0.92	0.95	0.99
Mg (mg/dL) (nl, 1.6-2.6)				1.7		1.7		1.6	1.6	1.6
PO4 (mg/dL) (nl, 2.7-4.6)				4.4	**5.3**		**8.9**	**7.1**	**5.9**	**8.8**
25-OHD (ng/dL) (nl, 25-100)				27		47	61			
TSH (mIU/L) (nl, 0.30-5.50)			2.24				0.78			
24-hour urine calcium (mg) (nl, 100-300)					112					

Laboratory values at 9 years to 1 week before, and 2 weeks to 6 months after surgery. Values in bold text are out of range. yr = year; m = month; w = week; PTH = parathyroid hormone; Cr = creatinine; Mg = magnesium; PO4 = phosphate; 25-OHD = 25-hydroxyvitamin D; TSH = thyroid stimulating hormone