Case Report

DOI: 10.4274/jcrpe.galenos.2026.2025-10-19

Short Stature and Growth Hormone Deficiency in POMC Deficiency: An Unexpected Clinical Association

Uğur Cem Yılmaz, Deniz Özalp Kızılay, Damla Gökşen, Samim Özen
Ege University Faculty of Medicine, Department of Pediatric Endocrinology and Diabetes, Bornova, İzmir, Türkiye

What is already known on this topic?
Proopiomelanocortin (POMC) deficiency is a rare monogenic obesity syndrome characterized by adrenal insufficiency, early-onset obesity, red hair, and hypopigmentation. Although multiple hypothalamic–pituitary hormone abnormalities have been described, linear growth is usually preserved and growth hormone deficiency is considered uncommon.

What this study adds?
This report describes short stature with biochemically confirmed growth hormone deficiency in an adolescent girl with genetically confirmed POMC deficiency. It expands the clinical spectrum of the disorder, demonstrates a notable early growth response to growth hormone therapy, and highlights the importance of longitudinal growth and endocrine monitoring in individuals with POMC deficiency.

Abstract
Proopiomelanocortin (POMC) deficiency is a rare monogenic obesity syndrome typically characterized by early-onset obesity, red hair, and hypopigmentation, while linear growth is usually preserved. We report an adolescent girl with genetically confirmed POMC deficiency who developed short stature with biochemically confirmed growth hormone deficiency (GHD). She was diagnosed at 3.5 years of age with a homozygous c.64delA (p.Thr22Leufs*29) variant. Progressive growth deceleration became apparent after 12 years of age. At 13 years, her weight was 56.7 kg (+0.8 SDS), height was 143.0 cm (−2.5 SDS), and BMI was 27.1 kg/m² (+2.0 SDS). Growth velocity was 1.64 cm/year (−1.61 SDS), and pubertal stage was Tanner I. At 14 years of age, bone age was 10 years. IGF-1 was low at 82.8 µg/L (SDS: −2.28), and IGFBP-3 was 2.3 mg/L (SDS: −3.84). After euthyroidism had been achieved and estrogen priming had been completed, GH stimulation testing with L-DOPA and clonidine showed peak GH levels of 0.52 and 1.0 µg/L, respectively. Pituitary MRI was normal. Recombinant GH therapy (0.035 mg/kg/day) was initiated at 14 years 3 months. After 9 months, height increased to 150.2 cm (−1.95 SDS), BMI was 26.51 kg/m² (+1.79 SDS), and growth velocity improved to 11.29 cm/year, with no adverse events during follow-up. This case expands the clinical spectrum of POMC deficiency by demonstrating short stature with biochemically confirmed GHD and a notable early growth response to GH therapy. Further studies are needed to clarify the underlying mechanisms and to guide follow-up and management.
Keywords: POMC deficiency, short stature, growth hormone deficiency, hypothalamic-pituitary dysfunction, monogenic obesity

Uğur Cem Yılmaz, MD
Ege University Faculty of Medicine, Department of Pediatric Endocrinology and Diabetes, Bornova, İzmir, Türkiye
cmylmz12@gmail.com
https://orcid.org/0000-0002-5878-5731

20.10.2025
14.03.2026

Epub: 18.03.2026

Previous presentation: Previously presented at the Joint Congress of the European Society for Paediatric Endocrinology (ESPE) and the European Society of Endocrinology (ESE) 2025: Connecting Endocrinology Across the Life Course, Copenhagen, Denmark, 10-13 May 2025.

Introduction
Proopiomelanocortin (POMC) deficiency is a rare autosomal recessive disorder characterized by early-onset obesity, adrenal insufficiency, red hair, and hypopigmentation. The disorder results from pathogenic variants in the POMC gene, leading to impaired synthesis of peptides involved in hypothalamic regulation of appetite, energy balance, and adrenal function [1-5]. Although the metabolic and endocrine manifestations of POMC deficiency are well recognized, growth hormone deficiency (GHD) remains an uncommon and insufficiently characterized finding, with only a few reported cases [6,7]. We report an adolescent girl with genetically confirmed POMC deficiency who developed progressive growth failure and delayed puberty, ultimately leading to a diagnosis of GHD and initiation of growth hormone therapy. This case expands the clinical spectrum of POMC deficiency and highlights the importance of longitudinal growth and endocrine monitoring in affected individuals.

Case
A female patient, currently 15 years old, initially presented at the age of 3.5 years with rapid weight gain, obesity, recurrent hypoglycemia, and red hair. She was born at 38 weeks of gestation with a birth weight of 3100 grams. Her parents were first-degree cousins. During the neonatal period, she was treated for cholestasis and hypoglycemic seizures (serum glucose: 30 mg/dL). Weight gain began at 5.5 months of age, along with delay in neuromotor development.

At 3.5 years of age, her weight was 26 kg (SDS: +3.02), height 110 cm (SDS: +3.07), and BMI 21.5 kg/m² (SDS: +3.12). Laboratory evaluation revealed free T4: *0.76 ng/dL* (0.76–1.55), TSH: *6.89 µIU/mL* (0.35–5.5), morning fasting ACTH: *<10 pg/mL* (10–60), and cortisol: *0.01 µg/dL* (7–29). A CRH stimulation test revealed a suboptimal ACTH response (*baseline: 13 pg/mL*, *peak: 15 pg/mL*), and an ACTH stimulation test showed a maximal cortisol response of *0.08 µg/dL*.

The combination of early-onset obesity, adrenal insufficiency, central hypothyroidism, neuromotor delay, and ataxic gait led to the diagnosis of POMC deficiency. Cranial MRI and spectroscopy showed bilateral basal ganglia lesions secondary to neonatal hypoglycemia, with an elevated

lactate-lipid peak. Pituitary MRI was unremarkable. Hydrocortisone therapy (10 mg/m²/day) and levothyroxine (2 mcg/kg/day) were initiated. Genetic analysis confirmed a homozygous c.64delA (p.Thr22Leufs*29) variant in the *POMC gene.* This exon 1 frameshift variant introduces a premature stop codon and is predicted to abolish the production of functional POMC-derived peptides, thereby confirming the diagnosis in conjunction with the clinical phenotype.

The patient is beeing followed for epilepsy, antiepileptic-related thrombocytopenia, and an atrial septal defect (ASD). She also has a history of multiple hospitalizations due to seizures and lower respiratory tract infections.

The patient exhibited severe hyperphagia, characterized by an intense and persistent urge to eat, and became irritable or aggressive when food was delayed. Her family implemented strict dietary monitoring to prevent excessive weight gain. Annual follow-up assessments initially showed normal growth velocity. At 8.5 years of age (fifth year of follow-up), her weight was 50 kg (SDS: +3.09), height 135.3 cm (SDS: +1.05), and BMI 27.5 kg/m² (SDS: +2.8), with an annual height velocity of 5 cm/year. She remained prepubertal (Tanner stage A-P1M1). However, her growth velocity showed a progressive decline over time (Figure 1).

At 14 years of age (10th year of follow-up), the patient weighed 57 kg (SDS: +0.58), had a height of 145.5 cm (SDS: –2.56), and a BMI of 27.3 kg/m² (SDS: +2.0). Her annual growth velocity had declined to 3.7 cm/year. She had red hair and pale skin, with no clinical signs of insulin resistance such as acanthosis nigricans or striae. Pubertal assessment showed no pubic or axillary hair or breast development, consistent with Tanner stage 1, indicating delayed puberty. Laboratory testing revealed normal serum electrolytes, glucose, lipid profile, and liver function tests. Fasting insulin was elevated at 31.6 mU/L (2.6–10), and platelet count was low at 87,000/µL. Thyroid function tests were as follows: fT4 1.3 ng/dL (0.98–1.63), fT3 3.4 ng/L (2.56–5.01), TSH 3.77 mU/L (0.51–4.3), and prolactin 41.8 µg/L (4.79–23.3). Growth-related hormones showed reduced IGF-1 (82.8 µg/L; 146–480; SDS: −2.28) and IGFBP-3 (2.3 mg/L; 3.50–7.51; SDS: −3.84). Morning ACTH was <3 ng/L (7.2–63.3), and morning cortisol under hydrocortisone therapy was 0.48 µg/dL (4.82–19.5). Gonadotropins were: FSH 2.64 U/L, LH 0.73 U/L, estradiol <25 ng/L, and DHEAS <3 µg/dL (65.1–368). Bone age was significantly delayed (10 years at chronological age 14 years; Figure 1). Cranial MRI showed hyperintense signal areas in the bilateral cerebellar and cerebral hemispheres, possibly related to previous hypoglycemia. Pituitary MRI was normal. Pelvic ultrasonography revealed a prepubertal uterus and ovaries. GnRH stimulation test demonstrated FSH and LH responses approaching but not reaching pubertal levels, indicating incomplete activation of the hypothalamic-pituitary-gonadal axis. The patient's auxological, endocrine, imaging, and GnRH stimulation test findings are summarized in Table 1.

Given the presence of short stature and inadequate annual height velocity, growth hormone (GH) stimulation tests were conducted after achieving a euthyroid state and performing estrogen priming. In the L-DOPA test, the baseline GH concentration was 0.18 µg/L, increasing to 0.36 µg/L at 30 minutes, 0.49 µg/L at 60 minutes, 0.25 µg/L at 90 minutes, and peaking at 0.52 µg/L at 120 minutes. In the Clonidine test, baseline GH was 0.51 µg/L, followed by 0.18 µg/L at 30 minutes, 0.54 µg/L at 60 minutes, 1.0 µg/L at 90 minutes, and 0.92 µg/L at 120 minutes. Both tests demonstrated significantly blunted GH secretion, with peak levels not exceeding 1.0 µg/L, consistent with GH deficiency. Detailed GH stimulation test data are also provided in Table 1.

Pituitary MRI demonstrated normal gland size and morphology, with no evidence of structural abnormalities. Based on clinical and biochemical findings, recombinant growth hormone therapy was initiated at a dose of 0.035 mg/kg/day at the age of 14 years and 3 months. The patient exhibited excellent adherence to treatment, and no adverse effects were reported throughout the therapy course.

At the 15-year follow-up, 9 months after initiating GH therapy, the patient exhibited a significant growth response. Her weight increased to 59.8 kg (SDS: 0.67), height reached 150.2 cm (SDS: -1.95), and BMI was recorded as 26.51 kg/m² (SDS: 1.79). Most notably, her annual growth velocity showed a significant improvement, increasing from a pre-treatment rate of 3.7 cm/year to 11.29 cm/year (SDS: +4.04) following nine months of GH therapy. This substantial response highlights the effectiveness of GH replacement in addressing her growth impairment.

Discussion

This case of POMC deficiency was initially identified at 3.5 years of age, presenting with adrenal insufficiency, early-onset severe obesity, red hair, and neuromotor delay. The same report highlighted additional findings that had not been previously reported in the literature, including hyperintense basal ganglia lesions on brain MRI and neuromotor delay. The present report describes further clinical features observed during adolescence, shedding light on the long-term effects of POMC deficiency [8].

Our patient harbored a homozygous c.64delA (p.Thr22Leufs*29) POMC variant, which has previously been reported in association with early-onset adrenal insufficiency, neonatal hypoglycemia, hyperphagia, and obesity [8]. In the present report, we expand the clinical phenotype associated with this variant by describing short stature with biochemically confirmed growth hormone deficiency and delayed puberty during adolescence.

POMC deficiency has also been associated with delayed puberty and hypogonadotropic hypogonadism [3,5,6,9]. Previous reports have described delayed or absent pubertal development in affected individuals, supporting a role for POMC in the hypothalamic regulation of pubertal function. Consistent with these findings, our patient exhibited delayed puberty and hypogonadotropic hypogonadism, highlighting the importance of longitudinal endocrine follow-up and timely intervention.

Reported cases of POMC deficiency with growth hormone deficiency are summarized in Table 2 [1,6]. Clément et al. described a female patient with delayed puberty and growth hormone deficiency who achieved normal adult height after GH therapy initiated at 13.6 years, whereas Gregoric et al. reported a male patient with marked growth deceleration and biochemically confirmed growth hormone deficiency who ultimately attained adult height without GH treatment [1,6]. Although growth hormone deficiency has traditionally been regarded as an uncommon feature of POMC deficiency, recent evidence suggests that this association may be underrecognized and may occur within a broader spectrum of pituitary hormone deficiencies in individuals with biallelic POMC variants [6,7]. Our case adds to this limited literature by demonstrating severe biochemical growth hormone deficiency, delayed puberty, and a marked increase in height velocity following GH therapy.

In addition, recent evidence suggests that growth hormone deficiency in individuals with biallelic POMC variants may emerge over time as part of a broader pituitary hormone deficiency spectrum [7]. This highlights the importance of longitudinal auxological follow-up and careful endocrine evaluation in patients with POMC deficiency, particularly when growth deceleration, delayed puberty, or other evolving pituitary hormone abnormalities are present.

The underlying mechanism of GHD in POMC deficiency remains unclear. Although this association may be coincidental, severe hypoglycemic episodes during early infancy may have disrupted hypothalamic-pituitary development and contributed to impaired GH secretion in our patient. The normal pituitary MRI findings suggest that the impaired GH secretion is likely due to a functional neuroendocrine disruption rather than a structural defect. Given the rarity of this finding, further studies are needed to clarify whether POMC-related pathways directly influence GH secretion or whether GHD develops secondarily to metabolic or hypothalamic dysfunction.

Following GH therapy, a significant increase in annual growth velocity was observed, indicating a strong response to treatment. However, long-term follow-up is necessary to determine whether the patient will achieve the expected final adult height. Further studies are also needed to evaluate the long-term effects of GH therapy in individuals with POMC deficiency.

Setmelanotide, an MC4R agonist, is an important targeted treatment option for POMC deficiency, particularly for the management of hyperphagia and obesity [10,11]. However, our patient has not received this therapy, and the present report therefore focuses on growth hormone deficiency and growth response.

Conclusion

This case highlights key findings from the long-term follow-up of a patient with POMC deficiency. Delayed puberty and hypogonadotropic hypogonadism were documented, along with short stature—a rare manifestation that broadens the recognized clinical phenotype of this condition. Growth hormone therapy significantly improved annual growth velocity, underscoring its effectiveness in addressing growth failure.

Although short stature is not typically associated with POMC deficiency, this case suggests that GH deficiency may occur as a rare but clinically meaningful component. The potential contribution of early-life hypoglycemia to hypothalamic-pituitary dysfunction and subsequent GH deficiency merits further investigation. Given this possibility, systematic evaluation of growth parameters should be considered in individuals with POMC deficiency, particularly in those with unexplained short stature.

The observed positive response to GH therapy reinforces its therapeutic role in managing growth impairment in this population. Early diagnosis, timely intervention, and close monitoring are essential to optimize growth outcomes and provide comprehensive care. Furthermore, recent literature indicates that GH deficiency may be a more frequent endocrine feature in biallelic POMC deficiency than previously recognized, highlighting the importance of routine assessment of the somatotropic axis in affected individuals.

Patient and Parent Perspective

The patient and their parents reported a noticeable improvement in growth velocity and overall well-being following growth hormone therapy. While they initially expressed some concerns regarding the treatment, it was well tolerated, and the observed improvements in physical development provided reassurance and motivation for continued therapy.

Ethics and Consent

Written informed consent was obtained from the patient's parents/legal guardians for the publication of this case report, including clinical information and diagnostic images. All potentially identifying information was removed to protect confidentiality. The report was prepared in accordance with the Declaration of Helsinki and institutional ethical standards for case report publication.

Clinical trial registration

Not applicable.

Author Contributions

UCY conceived and designed the study. UCY, DOK, DG, and SO acquired and interpreted the clinical data. UCY drafted the initial manuscript; all authors critically revised and approved the final version. UCY, DOK, DG, and SO take responsibility for the accuracy and integrity of the data.

Funding

This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of Interest

The authors declare that they have no conflicts of interest relevant to the content of this case report.

Acknowledgments

We sincerely thank the patient and their family for their cooperation and support in the preparation of this case report.

Data Availability Statement

The data supporting the findings of this case report are not publicly available due to patient privacy and confidentiality considerations. However, additional information may be provided by the corresponding author upon reasonable request and in accordance with institutional ethical guidelines.

References

1. Clément K, Dubern B, Mencarelli M, Słupecka-Ziemilska M. Unexpected endocrine features and normal pigmentation in a young adult patient carrying a novel homozygous mutation in the POMC gene. J Clin Endocrinol Metab. 2008;93(11):4521–6. https://doi.org/10.1210/jc.2008-1164
2. Krude H, Biebermann H. Obesity due to proopiomelanocortin deficiency: three new cases and treatment trials with thyroid hormone and ACTH4–10. J Clin Endocrinol Metab. 2003;88(10):4633–40. https://doi.org/10.1210/jc.2003-030502
3. Krude H, Biebermann H, Luck W, Horn R, Brabant G, Gruters A. Severe early-onset obesity, adrenal insufficiency, and red hair pigmentation caused by POMC mutations in humans. Nat Genet. 1998;19(2):155–7. https://doi.org/10.1038/509
4. Farooqi IS, O'Rahilly S. Genetics of obesity in humans. Endocr Rev. 2008;29(7):689–703. https://doi.org/10.1210/er.2006-0040
5. Mendiratta MS, Yang Y, Balazs AE, Willis AS. Early onset obesity and adrenal insufficiency associated with a homozygous POMC mutation. Int J Endocrinol. 2011;2011:705426. https://doi.org/10.1186/1687-9856-2011-5
6. Gregoric N, Groselj U, Bratina N, Debeljak M, Zerjav Tansek M, Suput Omladic J, et al. Two cases with an early presented proopiomelanocortin deficiency: a long-term follow-up and systematic literature review. Front Endocrinol (Lausanne). 2021;12:689387. https://doi.org/10.3389/fendo.2021.689387
7. Vitellius G, Poitou C, Clément K, Petit JM, Gatta-Cherifi B, Amanzougarene S, et al. Biallelic pathogenic variants in POMC can cause combined pituitary hormonal deficiency associated with severe obesity. Eur J Endocrinol. 2025;193(1):31–8. https://doi.org/10.1093/ejendo/lvaf127
8. Özen S, Özcan N, Uçar SK, Gökşen D. Unexpected clinical features in a female patient with proopiomelanocortin (POMC) deficiency. J Pediatr Endocrinol Metab. 2015;28(7-8):853–7. https://doi.org/10.1515/jpem-2014-0324
9. Kühnen P, Clément K, Wiegand S, Blankenstein O, Gottesdiener K, Martini LL, et al. Proopiomelanocortin deficiency treated with a melanocortin-4 receptor agonist. N Engl J Med. 2016;375(3):240–6. https://doi.org/10.1056/NEJMoa1512693
10. Clément K, van den Akker E, Argente J, Bahm A, Chung WK, Connors H, et al. Efficacy and safety of setmelanotide, an MC4R agonist, in individuals with severe obesity due to LEPR or POMC deficiency: single-arm, open-label, multicentre, phase 3 trials. Lancet Diabetes Endocrinol. 2020;8(12):960–70. https://doi.org/10.1016/S2213-8587(20)30364-8
11. Faccioli N, Poitou C, Clément K, Dubern B. Current treatments for patients with genetic obesity. J Clin Res Pediatr Endocrinol. 2023;15(2):108–19. https://doi.org/10.4274/jcrpe.galenos.2023.2023-3-2
12. Kahveci A, Kurt I, Turan S, Guran T, Bereket A, Haliloglu B. Real-life experience on efficacy and safety of setmelanotide treatment in prepubertal children. Eur J Endocrinol. 2025;192(2):K15–8. https://doi.org/10.1093/ejendo/lvaf008

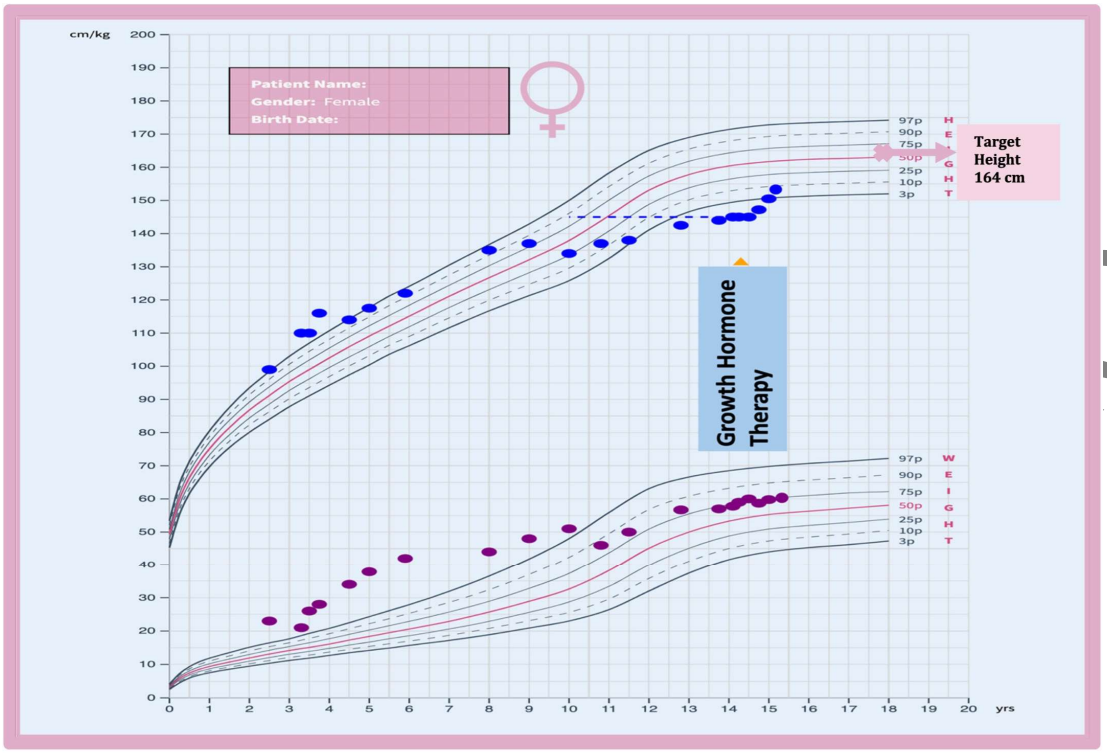

Figure 1. Growth chart
Alt Text (Figure 1): The growth chart illustrates the follow-up of a girl with POMC deficiency from birth to 15 years of age. While initial growth velocity was within the normal range, a marked decline occurred after age 8, reaching a height SDS of –2.56 at age 14. Following initiation of growth hormone therapy, annual growth velocity improved significantly and the curve shifted toward the target height.

Table 1. Auxological, endocrine, stimulation, imaging, and treatment response findings of the patient

Parameter	**Result**	**Reference Range**
Clinical and Auxological Data		
Age at evaluation	14 years	
Height (SDS)	145.5 cm (−2.56)	
Weight (SDS)	57 kg (+0.58)	
BMI, kg/m^2 (SDS)	27.3 (+2.0)	
Growth velocity	3.7 cm/year	
Pubertal stage (Tanner)	Stage 1	
Bone age	10 years (CA: 14 years)	
Basal Endocrine Evaluation		
fT4, ng/dL	1.3	0.98–1.63
fT3, ng/L	3.4	2.56–5.01
TSH, mU/L	3.77	0.51–4.3
Prolactin, µg/L	41.8	4.79–23.3
IGF-1, µg/L (SDS)	82.8 (−2.28)	146–480
IGFBP-3, mg/L (SDS)	2.3 (−3.84)	3.50–7.51
Fasting insulin, mU/L	31.6	2.6–10
Morning ACTH, ng/L*	<3	7.2–63.3
Morning cortisol, µg/dL*	0.48	4.82–19.5
FSH, U/L	2.64	

LH, U/L	0.73	
Estradiol, ng/L	<25	
DHEAS, µg/dL	<3	65.1–368
GnRH Stimulation Test		
	FSH (U/L)	**LH (U/L)**
Baseline (0 min)	2.43	0.412
30 min	6.70	6.03
60 min	7.19	4.98
90 min	7.14	4.07
Peak response	**7.19**	**6.03**
GH Stimulation Tests (after estrogen priming)		
	L-DOPA (µg/L)	**Clonidine (µg/L)**
Baseline (0 min)	0.18	0.51
30 min	0.36	0.18
60 min	0.49	0.54
90 min	0.25	1.0
120 min	0.52	0.92
Peak GH	**0.52**	**1.0**
Imaging		
Pituitary MRI	Normal size and morphology; no structural abnormality	
Pelvic ultrasonography	Prepubertal uterus and ovaries	
GH Treatment Response (9 months)		
	Pre-treatment	**Post-treatment**
GH dose	—	0.035 mg/kg/day
Height, cm (SDS)	145.5 (−2.56)	150.2 (−1.95)
Weight, kg (SDS)	57 (+0.58)	59.8 (+0.67)
BMI, kg/m^2 (SDS)	27.3 (+2.0)	26.51 (+1.79)
Growth velocity, cm/year	3.7	11.29 (+4.04)

[*] *Measured while the patient was receiving hydrocortisone replacement therapy.*
Abbreviations: ACTH, adrenocorticotropic hormone; BMI, body mass index; CA, chronological age; DHEAS, dehydroepiandrosterone sulfate; FSH, follicle-stimulating hormone; GH, growth hormone; GnRH, gonadotropin-releasing hormone; IGF-1, insulin-like growth factor 1; IGFBP-3, insulin-like growth factor binding protein 3; LH, luteinizing hormone; MRI, magnetic resonance imaging; SDS, standard deviation score; TSH, thyroid-stimulating hormone.

Table 2. Reported cases of POMC deficiency with growth hormone deficiency and growth outcomes

Study	Sex	POMC Variant	Age at GHD Diagnosis / Evaluation	Growth Findings	Peak GH Response	GH Treatment	Growth Outcome	Final Height
Clément et al., 2008	F	Homozygous c.223dupC (p.Arg75fs)	13.5 y	HV 1.5 cm/y (ages 11–13.5)	Arginine-insulin: 4.3 µg/L	Yes; 23 µg/kg/day from 13.6 y	Normal adult height achieved	168 cm
Gregoric et al., 2021	M	Compound het. c.151A>T (p.Lys51*) / c.296delG (p.Gly99fs)	≈14 y	95th→10th percentile in 5 y; BA 9 y 4 mo at CA 14 y	Arginine: 2.76 µg/L; L-DOPA: 1.76 µg/L	No	Catch-up growth with spontaneous puberty	183 cm

Present case	F	Homozygous c.64delA (p.Thr22Leufs*29)	14 y	Height −2.56 SDS; HV 3.7 cm/y; BA 10 y at CA 14 y	L-DOPA: 0.52 µg/L; clonidine: 1.0 µg/L	Yes; 0.035 mg/kg/day from 14 y 3 mo	HV increased from 3.7 to 11.29 cm/y after 9 mo of GH therapy	Not yet available
Abbreviations: BA, bone age; CA, chronological age; F, female; GHD, growth hormone deficiency; het., heterozygous; HV, height velocity; M, male; mo, months; POMC, proopiomelanocortin; SDS, standard deviation score; y, years.								