



Evaluation of growth and puberty in a child with a novel *TBX19* gene mutation and review of the literature

Zehra Yavas Abali¹ · Gozde Yesil² · Tarik Kirkgoz¹ · Sare Betul Kaygusuz¹ · Mehmet Eltan¹ · Serap Turan¹ · Abdullah Bereket¹ · Tulay Guran¹

Received: 10 November 2018 / Accepted: 31 January 2019 / Published online: 12 February 2019
© Hellenic Endocrine Society 2019

Abstract

Background Biallelic mutations in the *TBX19* gene cause severe early-onset adrenal failure due to isolated ACTH deficiency (IAD). This rare disease is characterized by low plasma ACTH and cortisol levels, with normal secretion of other pituitary hormones. Herein, we report a patient with IAD due to a novel *TBX19* gene mutation, who is also of tall stature.

Case report A 4^{8/12}-year-old girl was presented with loss of consciousness due to hypoglycemia. The patient was born at term with a birth weight of 3800 g. Her parents were first-degree cousins. She had a history of several hospitalizations for recurrent seizures, abdominal pain, and vomiting. At presentation, her weight and height were +1.8 and +2.2 SDS, respectively. Serum glucose was 25 mg/dl (1.4 mmol/L), with normal sodium, potassium, and insulin concentrations. The child was hypocortisolemic (0.1 µg/dl), and ACTH levels were extremely low (<5.0 pg/ml). A diagnosis of IAD was made and hydrocortisone treatment was started. Hypoglycemic episodes, seizures, and recurrent gastrointestinal complaints disappeared after hydrocortisone replacement. Magnetic resonance imaging of the pituitary was normal. Whole exome sequencing revealed a novel homozygous c.302G > A (W101*) mutation in the *TBX19* gene.

Conclusion We report a new mutation in the *TBX19* gene in a patient with isolated ACTH deficiency. While overgrowth is a known feature of some types of adrenal insufficiencies, including *MC2R* gene defects and POMC deficiency, it may be a novel feature for TPIT deficiency, as in our patient.

Keywords TPIT · *TBX19* · Isolated ACTH deficiency · Growth · Puberty · Central adrenal insufficiency

Introduction

Adrenocorticotrophic hormone (ACTH) is required for the synthesis of glucocorticoids and adrenal sex steroids. Impaired synthesis of ACTH from any genetic or acquired cause may result in secondary adrenal insufficiency. Congenital isolated ACTH deficiency (IAD) (MIM #201400) is characterized by low plasma ACTH and cortisol levels without deficiency of other pituitary hormones [1]. Recessively inherited mutations in the *TBX19* gene are reported to cause IAD. T-box factor 19

(*TBX19*) is the first T-box gene identified in the pituitary, and encodes T-box pituitary restricted transcription factor (TPIT). TPIT is important for both proopiomelanocortin (POMC) gene expression and differentiation of cells expressing POMC [2]. In the absence of TPIT, intermediate lobe melanotropes and corticotropes (POMC lineages) fail to differentiate. Furthermore, inactivation of this transcription factor results in the change of cell fate and in melanotropes differentiating into gonadotropes in mice [2–4].

The *TBX19* gene (MIM*604614) is located in chromosome 1q24.2, consisting of 8 exons, and mutations of this gene are associated with early-onset IAD in humans [4, 5]. IAD associated with *TBX19* gene mutations is very rare, with 25 different mutations having been described so far [6]. Patients with *TBX19* gene defects usually present with severe ACTH deficiency and adrenal insufficiency in the neonatal period or early childhood. Hypoglycemia and prolonged jaundice are frequently observed, and death may result if not diagnosed early. The pituitary gland is structurally normal [2, 7].

✉ Tulay Guran
tulayguran@yahoo.com

¹ Department of Pediatric Endocrinology and Diabetes, Marmara University School of Medicine, Istanbul, Turkey

² Department of Medical Genetics, Bezmialem Vakıf University School of Medicine, Istanbul, Turkey

However, pituitary function other than ACTH deficiency has not been reported in detail in previous studies.

Herein, we report a patient with congenital IAD due to a novel *TBX19* gene mutation. In addition to early-onset IAD, she also had accelerated growth, which is discussed in light of the current literature on TPIT deficiency.

Case report

A 4^{8/12}-year-old girl was admitted to the pediatric emergency unit with loss of consciousness. She was found to be hypoglycemic, with a capillary glucose level of 25 mg/dl (1.4 mmol/L). Past medical history revealed that she was born at term with a birth weight of 3800 g (+1.6 SDS) and was hospitalized for 10 days in a neonatal care unit for respiratory distress and hyperbilirubinemia. Her parents were first-degree cousins (Fig. 1a). Her brother died on the 23rd third postnatal day of unknown causes, and a preterm born sister died on the postnatal day after esophageal atresia surgery. Her mother had also lost a male fetus during the second trimester of unclear causes. Maternal prenatal evaluation and ultrasound imaging were unremarkable. The patient had not begun to walk until

the age of 2, while first tooth eruption was also delayed (at 18 months). She was reported as having frequent viral respiratory tract infections and also a history of emergency department admissions due to vomiting, abdominal pain, and diarrhea. At about 3 years of age, she had recurrent seizures, especially in the morning. She was hospitalized in a pediatric intensive care unit with loss of consciousness and hypoglycemia at the age of 4. Hypoglycemic episodes were diagnosed as ketotic hypoglycemia after prolonged fasting.

At presentation to our clinic at the age of 4^{8/12} years, her weight and height were 23.1 kg (+1.8 SDS) and 116.5 cm (+2.2 SDS), respectively, despite having a midparental target height of -0.8 SDS. She had no facial dysmorphism, hypo/hyperpigmentation, or red hair. Cardiac and abdominal examination was normal. Her pubic and breast stage were Tanner I. At initial evaluation, her developmental milestones were delayed compared to chronological age, while fine motor skills were appropriate for her age. Laboratory investigations in the emergency unit confirmed hypoglycemia and serum glucose 25 mg/dl (1.4 mmol/L), with normal sodium and potassium levels, mildly elevated AST (66 U/L), and normal ALT, creatinine, and bilirubin. Capillary ketone level was 2.2 mmol/L, while serum insulin and C-peptide were

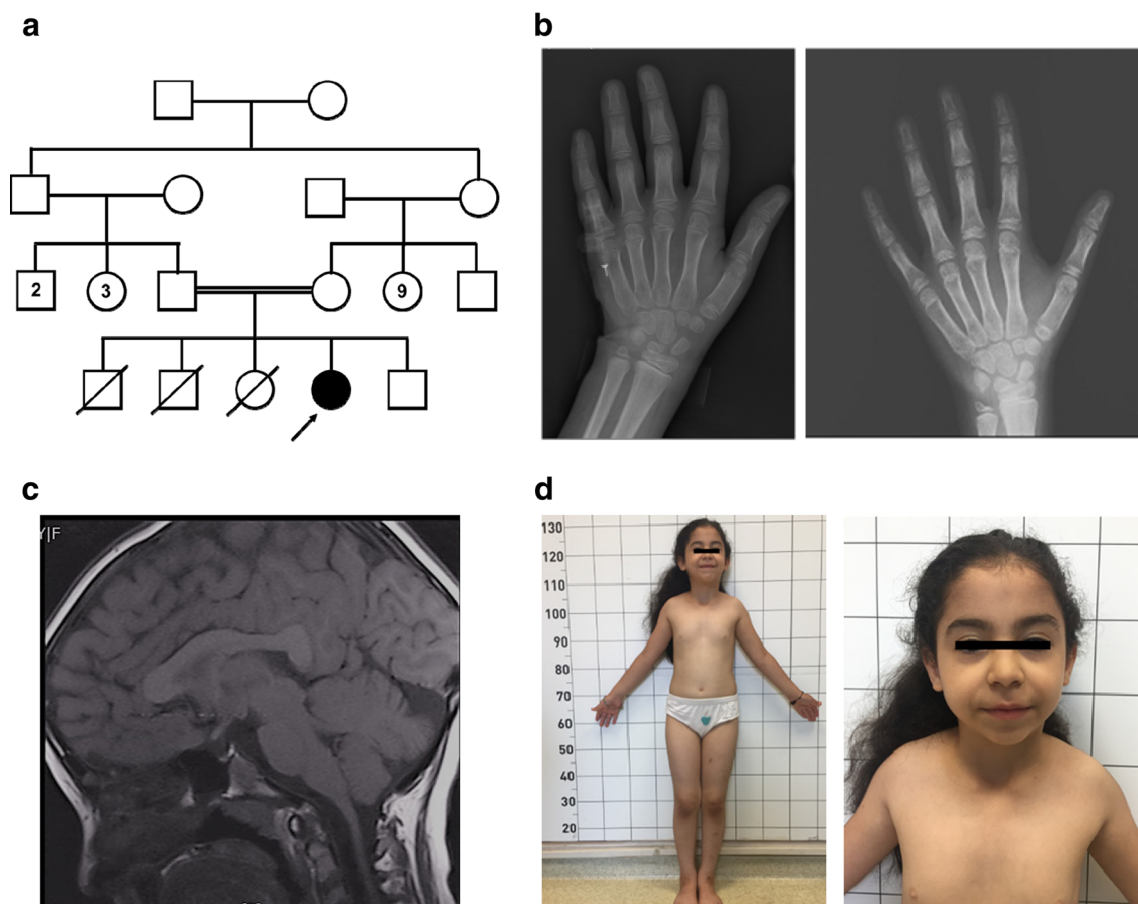


Fig. 1 The pedigree (a), the pituitary MRI (b), bone age at 4^{9/12} and 6^{9/12} years of age (c), and phenotypic appearance at last clinical visit (d) of our patient

undetectable; hence, hyperinsulinemia was excluded. Blood lactate (0.7 mmol/L) and ammonia (20.1 $\mu\text{mol/L}$) were normal and she had no metabolic acidosis. The child was hypocortisolemic (0.1 $\mu\text{g/dl}$) with an extremely low ACTH level (< 5.0 pg/ml (0–46)). Other anterior pituitary hormones were normal (growth hormone 14.8 $\mu\text{g/L}$) at the time of hypoglycemia. Serum amino acids and urinary organic acid profile were normal. Insufficient cortisol response (0.4 $\mu\text{g/dl}$) was detected in the low-dose (1 μg intravenous) ACTH stimulation test. Diagnosis of central adrenal insufficiency due to ACTH deficiency was made, and hydrocortisone treatment (10 mg/m²/day in three divided doses) was started. Her hypoglycemic episodes and recurrent infections disappeared after hydrocortisone replacement. Magnetic resonance imaging of the pituitary was normal (Fig. 1b). Whole exome sequencing revealed a novel homozygous c.302G > A (W101*) mutation in the *TBX19* gene, producing a truncated protein.

In the first year of follow-up, her height was + 1.6 SDS. Her pubic and breast stages were Tanner I. At the age of 5^{4/12} years, she had Tanner 2 breast development with advanced bone age (7.8 years) (Fig. 1c) and high basal serum LH value (0.63 mIU/ml). Pelvic USG revealed enlarged ovaries (right: 33 × 17 × 12 mm, left: 25 × 16 × 15 mm) and uterus volume was 33 × 10 × 6 mm. However, an LHRH stimulation test result was in the prepubertal range (peak LH: 2.35 mIU/ml and peak FSH: 11.4 mIU/ml). The patient was observed for the tempo of puberty, and her breast stage was regressed during follow-up.

She was also investigated because of her being in the upper centiles of the growth chart and tall for target height, despite having had several vomiting/diarrhea and hypoglycemia episodes in the past. Her IGF-1 and IGFBP3 values were < 25.0 ng/ml (50–303) and 1.02 $\mu\text{g/ml}$ (1.1–6.1), respectively, not suggestive of the etiology of overgrowth. Reevaluation of whole exome sequencing data revealed no pathogenic variant in the *MC2R* gene.

She was normoglycemic during 2.5-years of follow-up with hydrocortisone replacement (10 mg/m²/day), during which period the patient had no record of infections and no need for hospitalizations. At her last visit at the age of 7^{1/12} years (Fig. 1c), her weight and height were 28.7 kg (+ 1.3 SDS) and 126.1 cm (+ 0.9 SDS), respectively. Systemic evaluation was normal, apart from breast stage Tanner 2. Her bone age was still 7.8 years, and basal serum LH value was 0.37 mIU/ml. The ovaries were enlarged (right: 28 × 25 × 11 mm, left: 22 × 17 × 13 mm) for her age, and uterus volume was 33 × 23 × 10 mm. Peak LH and FSH levels in repeated LHRH stimulation testing were 5.78 mIU/ml and 11.5 mIU/ml, respectively. However, height velocity was 3.2 cm/year and bone age was not progressive. Other anterior pituitary hormone levels were also normal during follow-up. GH, IGF-1, and IGFBP3 values were 0.47 ng/ml (0–10), 76.8 ng/ml (80–233), and 3.0 $\mu\text{g/ml}$ (1.4–6.1), respectively.

Clinical and laboratory findings of the patient at diagnosis and last evaluation are illustrated in Table 1.

Hormonal assays

Serum cortisol concentrations were analyzed by commercial kits based on electrochemiluminescence immunoassay (Beckman Coulter, USA). Plasma ACTH concentrations were analyzed by two-site sequential chemiluminescent immunoassay (Immulite 2000, Siemens). IGF-1 and IGFBP3 were analyzed by immunoassay (Immulite 2000, Siemens). LH and estradiol (E2) were analyzed by electrochemiluminescence immunoassay method (ECLIA) (Cobas e601, Roche). FSH concentrations were analyzed by electrochemiluminescence immunoassay (Beckman Coulter, USA).

Table 1 Clinical and laboratory findings of the patient at diagnosis and last evaluation

	At presentation	At last evaluation
Age (years)	4 ^{8/12}	7 ^{1/12}
Weight (kg)/SDS	23.1/+ 1.8	28.7/+ 1.3
Height (cm)/SDS	116.5/+ 2.2	126.1/+ 0.9
BMI SDS	+ 1.0	1.1
Bone age (years)	7.8	7.8
Mother's height (SDS)	− 1.6	− 1.6
Father's height (SDS)	− 0.2	− 0.2
Target height SDS	− 0.8	− 0.8
Tanner stage (breast/pubertal hair)	(I/I)	(II/I)
Laboratory evaluation		
Serum glucose (mmol/L)	1.4	4.0
Na (mmol/L)/K (mmol/L)	135/4.5	143/4.3
Blood gases PH/HCO ₃	7.38/25.8	7.3/24.8
Insulin (2.6–24.9 $\mu\text{IU/ml}$)	0.2	–
ACTH (0–46 pg/ml)	< 5.0	< 5.0
Cortisol (5–25 $\mu\text{g/dl}$)	0.1	0.53
Prolactin (4.1–18.4 ng/ml)	23.1	19.0
FT4 (0.61–1.12 ng/dl)	1.1	0.97
TSH (0.34–5.6 $\mu\text{IU/L}$)	6.1	4.27
Peak cortisol response (low-dose ACTH test) ($\mu\text{g/dl}$)	0.4	
Growth hormone (0–10 ng/ml)	NA	0.47
IGF-1* (ng/ml)	< 25	76.8
IGFBP3* ($\mu\text{g/ml}$)	1.02	3.0

ACTH adrenocorticotrophic hormone, FT4 free thyroxine, TSH thyroid-stimulating hormone, IGF-1 insulin-like growth factor-1, IGFBP3 insulin-like growth factor binding protein 3, NA not available

IGF1*: ranges for 4^{8/12} and 7^{1/12} years of age are (50–303) and 80–233 ng/ml, respectively

IGFBP3*: ranges for 4^{8/12} and 7^{1/12} years of age are (1.1–6.1) and (1.4–6.1) ($\mu\text{g/ml}$), respectively

Molecular analyses

Written informed consent was obtained from the parents. DNA was extracted from peripheral blood using DNeasy blood extraction kits based on the manufacturer's protocol (QIAGEN, <http://www.qiagen.com/>). Genomic DNA from the patient and family was sequenced and analyzed at Bezmialem Medical Faculty Department of Medical Genetics Molecular Laboratory. Amplified PCR samples were used for generating gene libraries by Nextera Rapid Capture Enrichment (Illumina, USA) kit protocol. Exome sequencing was performed on the NextSeq500 platform. Critical variants were analyzed using Illumina Variant Studio, and pathogenicity of the candidate variants was evaluated using Alamut Visual and HGMD Professional databases. As the parents were consanguineous, we initially filtered homozygous rare variants with a minor allele frequency of <0.01 in the 1000 Genomes Project data (<http://www.1000genomes.org/>), searching for autosomal recessive inheritance. Whole exome sequencing revealed a novel homozygous c.302 G > A change predicting a termination codon in the 101st aminoacid position in the *TBX19* gene. This variant was not detected in our in-house database, nor was it found in public databases, such as ExAC, dbSNP, ESP, and 1000 Genomes Project data. The variant was predicted to be disease-causing according to in silico software, including Polyphen-2, SIFT, and Mutationtaster [8–10]. Pathogenic or probable pathogenic variants in other adrenal insufficiency-related genes (*PITX*, *MC2R*, and *POMC*), and also overgrowth-related genes, were not detected.

Discussion

Congenital IAD is a rare and potentially life-threatening disease and may therefore be underestimated due to the low level of suspicion in clinical practice. As in our case, patients usually have several hospitalizations for hypoglycemia and episodes of abdominal pain and vomiting before the diagnosis is established. Thus, clinicians evaluating a hypoglycemic patient must consider the possibility of adrenal insufficiency and it is important to take critical samples of cortisol at the time of hypoglycemia. Congenital IAD is classified as early-onset (neonatal) and late-onset (juvenile) type, according to the onset of hypoglycemia. Metherell et al. [11] have defined onset within 1 year of age as early-onset IAD. Vallette Kasic et al. [2] have reported that the first symptoms appear in the neonatal period in all early-onset cases and the diagnosis is generally made between birth and 2 years of age. *TBX19* gene mutation was detected in most of the early-onset (neonatal) IAD cases, but not in juvenile onset cases. Thus, *TBX19* gene analysis is recommended, especially in IAD presenting in the neonatal period or early childhood [2, 11].

Hypoglycemia, seizures, and jaundice are the most common symptoms of IAD during the neonatal period [11–13]. Our patient had a history of neonatal hyperbilirubinemia but she had no cholestatic jaundice. A patient with compound heterozygous *TBX19* gene mutation, presenting with recurrent lower respiratory tract infections without hypoglycemia, was reported recently [14]. Our patient had frequent respiratory tract infections and was hypoglycemic at admission, as are many reported cases.

Clinical presentations of previously reported patients with congenital IAD due to *TBX19* gene mutations are summarized in Table 2. To date, 25 different *TBX19* gene mutations have been identified [6]. *TBX19* mutations are found throughout the gene, especially in the T-box region, resulting in DNA-binding defects [1]. In our patient, whole exome sequencing revealed a novel homozygous nonsense c.302 G > A (W101*) mutation localized in the T-box region of the *TBX19* gene. *TBX19* gene mutations identified in congenital IAD are illustrated in Fig. 2.

There are a limited number of reports about prenatal diagnosis of IAD by low estriol levels in maternal serum triple marker screening [16–18]. Low estriol levels with normal fetal ultrasonography and exclusion of placental sulfatase deficiency and Smith-Lemli-Opitz (SLO) syndrome may suggest a defect in fetal steroidogenesis. Weintrob et al. [18] reported a patient with low estriol in maternal serum triple screening with normal fetal sonography, who was diagnosed with ACTH deficiency postnatally. Subsequently, the patient was found to have a novel *TBX19* gene mutation and was treated with hydrocortisone. Our case also had a history of intrauterine death of a sibling and postnatal death of two siblings of unknown causes. Her mother had been followed by an obstetrician and she had amniocentesis for the history of the deaths of unknown etiology of her three children. Results were reportedly “normal.” Awareness about the low estriol observed in relation to adrenal insufficiency may increase the number of patients with prenatal and early diagnosis of IAD.

Despite severe hypoglycemic episodes and recurrent infections and hospitalizations, our patient had accelerated growth. Furthermore, she had low IGF1 and insulin levels. On follow-up, she was observed to have premature thelarche, but did not develop progressive precocious puberty which would have accounted for the significant advancement of linear growth. Therefore, premature thelarche may only partially have contributed to growth phenotype in our case. Reports to date on the pubertal development of patients with *TBX19* mutations are inadequate. Animal studies report that TPIT is a negative regulator of gonadotroph differentiation. Cells would switch to gonadotroph cell line in the case of *TBX19* gene inactivation [4, 5]. TPIT-deficient mice had mildly increased levels of gonadotroph cells in the intermediate and anterior lobe of the pituitary. Nevertheless, an increased number of gonadotrophs is not sufficient to affect gonadotroph function. The TPIT

Table 2 Clinical presentation and mutations of patients with congenital IAD patients due to *TBX19* gene mutations

Patient	Consanguinity	Familial case	Death of a sibling	Hypoglycemia	Seizure	Jaundice	Mutation	
1	+			+			R179*/R179*	
2	+		+	+		+	R286*/R286*	
3	+			+			delA/delA	
4	+			+			delA/delA	Pulichino [15] [‡]
5	+	+	+	+			T58A/T58A	
6	+	+	+	+			T58A/T58A	
7			+	+		+	S128F/del 5.2kb	
8	+		+	+			I171T/I171T	
9	–	+		+	+	+	Q28*/Q28*	
10	–	+		+	+	+	Q28*/Q28/*	
11	+	–		+		+	R179*/R179*	Vallette-Kasic [2] [‡]
12	+	+	+	+		+	R286*/R286*	
13	+			+	+	+	R286*/R286*	
14	+	+	+	+	+		T58A/T58A	
15	+	+	+	+			T58A/T58A	
16	–	+	+	+		+	S128F/del5.2 Kb	
17	–			+		+	I171T/I171T	
18	–			+	+	+	nt782delA/T195A	
19	+	+		+	+		nt782delA/nt782delA	
20	+	+		+	+		nt782delA/nt782delA	
21	–	+		+	+		nt782delA/nt782delA	
22	–	+		+			nt782delA/nt782delA	
23		NA					M86R/782delA	Metherell [11]
24							M86R/782delA	
25		–		+	+	+	R53fs/pR179*	Alsalem [12]
26			–	–	–	–	R53fs/pR179*	Akcan [14]
27	+	+		+	+	+	R286*/R286*	Unal [13]
28	+	–	+	+	+	–	W101*	Current case
29 to 66 [¥]	10	NA	7	All patients	16	21	R100H H125Y G132V K164R nt782delA/20kb del IVS1 + 1G > A IVS5 + 1G > A IVS5 + 5G > A IVS1–15 ins5bp	Couture [1] [‡]

NA not available

[‡] The studies reporting functional analysis of novel *TBX19* gene mutation

[¥] Couture et al. reported characteristics of 37 patients (29 to 66) with *TBX19* gene mutation

From 1 to 28th patient characteristics were described case by case

mutant proteins may additionally repress steroidogenic factor-1 transcriptional activity and, hence, prevent the cell fate change to gonadotrophs [2, 4]. Therefore, the effect of these mutations on the pituitary-gonadal axis is not obvious.

Tall stature was reported in two other cases with adrenal insufficiency, *MC2R* gene defects (which cause primary adrenal insufficiency), and POMC deficiency (which causes central adrenal insufficiency). *MC2R* is a G

protein-coupled receptor and ACTH exerts its role through this receptor [19, 20]. Familial glucocorticoid deficiency (FGD) type 1 caused by *MC2R* mutations presents with primary adrenal insufficiency [21]. Additionally, FGD-1 cases have been reported with tall stature, the underlying mechanisms of which remain unclear. Bone growth is stimulated by IGF-binding protein 5 (IGFBP5). Glucocorticoids inhibit IGFBP5, and cortisol

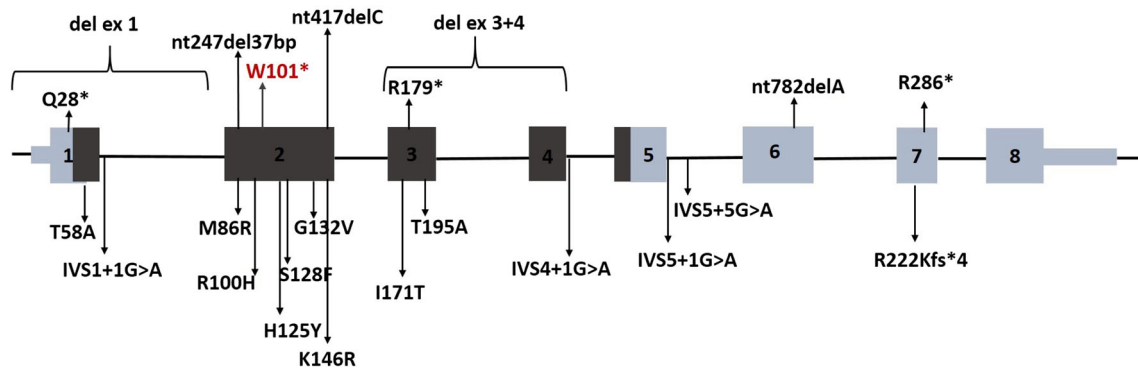


Fig. 2 Known *TBX19* mutations identified in isolated ACTH deficiency patients. Transcribed sequences are boxed. Small boxes include 5' and 3' untranslated regions. The coding sequence of *TBX19* gene is represented

by the bigger boxes. The dark gray boxes indicate the T-Box domain. The nonsense and deletional mutations are indicated at the upper part of the panel, missense and splice site mutations are shown in the lower panel

deficiency results in lack of negative inhibition. Tall stature in these patients may be related to this lack of inhibition of IGFBP5 [22–24]. Based upon previous reports, cortisol deficiency and lack of inhibition of IGFBP5 could, hypothetically, also be a mechanism underlying our case. A second hypothesis to explain tall stature in FGD-1 cases is the ACTH effect on the chondrogenic phenotype. In vitro, ACTH at high concentrations could activate melanocortin receptors in bone and the cartilaginous growth plate and stimulate growth. On the other hand, low ACTH in congenital IAD is incompatible with the mechanism of ACTH effect of chondrocytes. Any coexisting pathogenic variant of the *MC2R* gene was excluded in our patient in the WES analysis. It is suggested that glucocorticoid replacement normalizes advanced growth in FGD; however, the possibility of overtreatment is an issue [24]. In our case, height was in the upper

centiles, despite a declining trend from the 97th to 75th centile during follow-up.

Accelerated growth together with central adrenal insufficiency has also been observed in a few cases with POMC deficiency [25–27]. Although growth was not adequately described in these previous cases with POMC deficiency, obesity and hyperinsulinism were suspected to be causing growth acceleration [28]. However, Ozsu et al. [29] reported two siblings with overgrowth and POMC deficiency. One of them had insulinopenic diabetes and, hence, had low-normal serum IGF1 and low insulin concentrations. Therefore, regulation of accelerated linear growth with POMC deficiency, at least in this case, cannot be explained by hyperinsulinism.

Data in the literature about the growth and height potential of cases with *TBX19* gene mutations is limited. A case reported by Akcan et al. [14] concerned a prepubertal male

Table 3 Some anthropometric data of the patients with *TBX19* gene mutation reported so far

	Alsalem et al. [12]	Akcan et al. [14]	Unal et al. [13] [‡]		Current case
			Case 1	Case 2	
Gestational week	Term	Term	43	42	Term
Birth weight (g)	3800		3500	3500	3800
Type of delivery	NA	C/S	Spontaneous Vaginal	C/S	C/S
Gender (M/F)	M	M	M	F	F
Age at admission	11 days	34 months	2 months	7 days	4.7 years
Weight (kg)/weight SDS at admission	3.9/NA	17.2/+ 1.3	5.0/− 0.15	3.5/+ 0.47	23.1/+ 1.8
Height (cm)/height SDS at admission	NA	97.5/+ 0.5	56/+ 0.08	50/+ 0.28	116.5/+ 2.2
Age at last evaluation	20.5 months	7.2 years	5 years	10 months	7 years
Weight (kg)/weight SDS at last evaluation	NA	28.3/+ 1.1	20.7/+ 0.87	9.5/+ 0.57	28.7/+ 1.3
Height (cm)/height SDS at last evaluation	NA	123.7/+ 0.3	107/− 0.57	74/+ 0.54	126.1/+ 0.9
Mutation	R53fs/R179*	R53fs/R179*	R286*/R286*	R286*/R286*	W101*/W101*

NA not available, M male, F female, C/S cesarean section, SDS standard deviation score

[‡] Case 1 and Case 2 reported by Unal et al. were sibling

with compound heterozygous *TBX19* mutation, who was admitted at 3 years old with IAD. His height was +0.5 SDS at admission, and +0.3 SDS at last evaluation at the age of 7.2 years. In a recent study reporting two siblings with IAD due to *TBX19* gene mutation, their height and weight SDS were also in normal ranges, despite a history of hypoglycemic episodes and hospitalizations [13]. The anthropometric data of the patients with *TBX19* gene mutations reported so far are presented in Table 3.

In conclusion, we have reported a novel nonsense *TBX19* gene mutation. In addition to early-onset IAD, the patient had coexisting tall stature. While overgrowth is a known feature of various types of adrenal insufficiencies, including *MC2R* gene defects and POMC deficiency, it may be a novel feature of TPIT deficiency, as in our patient.

Acknowledgements The authors wish to express their gratitude to the parents and the patient who participated in this study.

Author contributions Zehra Yavas Abali, Gozde Yesil, Tarik Kirkgoz, Sare Betul Kaygusuz, Mehmet Eltan, Serap Turan, Abdullah Bereket, and Tulay Guran conceptualized and designed the study. Zehra Yavas Abali and Tulay Guran drafted the initial manuscript. Serap Turan, Abdullah Bereket, and Tulay Guran critically reviewed the manuscript. Gozde Yesil and Tulay Guran performed the assays, analyzed data, and interpreted the results. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Patient confidentiality The patient's parents provided informed consent for publication of the submitted article and the results of the accompanying genetic analyses.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

- Couture C, Saveanu A, Barlier A et al (2012) Phenotypic homogeneity and genotypic variability in a large series of congenital isolated ACTH-deficiency patients with TPIT gene mutations. *J Clin Endocrinol Metab* 97:486–495
- Vallette-Kasic S, Brue T, Pulichino AM et al (2005) Congenital isolated adrenocorticotropin deficiency: an underestimated cause of neonatal death explained by TPIT gene mutations. *J Clin Endocrinol Metab* 90:1323–1331
- Pulichino AM, Vallette-Kasic S, Couture C, Brue T, Drouin J (2004) Tpit mutations reveal a new model of pituitary differentiation and account for isolated ACTH deficiency. *Med Sci (Paris)* 20: 1009–1013
- Pulichino AM, Vallette-Kasic S, Tsai JP, Couture C, Gauthier Y, Drouin J (2003b) Tpit determines alternate fates during pituitary cell differentiation. *Genes Dev* 17:738–747
- Lamolet B, Pulichino AM, Lamonerie T et al (2001) A pituitary cell-restricted T box factor Tpit, activates POMC transcription in cooperation with Pitx homeoproteins. *Cell* 104:849–859
- Stenson PD, Mort M, Ball EV et al (2017) The human mutation database: towards a comprehensive repository of inherited mutation data for medical research, genetic diagnosis and next generation sequencing studies. *Hum Genet* 136:665–677
- Déchelotte P, Darcha C, Labbé A, Vanlieféringhen P, Beaufrère AM, Malpuech G (1994) Congenital adrenal hypoplasia due to isolated familial ACTH deficiency. *Pediatr Pathol* 14:377–380
- Adzhubei I, Jordan DM, Sunyaev SR (2013) Predicting functional effect of human missense mutations using PolyPhen-2. *Curr Protoc Hum Genet* 7:Unit7.20
- Sim NL, Kumar P, Hu J, Henikoff S, Schneider G, Ng PC (2012) SIFT web server: predicting effects of amino acid substitutions on proteins. *Nucleic Acids Res* 40:452–457
- Schwarz JM, Cooper DN, Schuelke M, Seelow D (2014) MutationTaster2: mutation prediction for the deep-sequencing age. *Nat Methods* 11:361–362
- Metherell LA, Savage MO, Dattani M et al (2004) TPIT mutations are associated with early onset, but not late-onset isolated ACTH deficiency. *Eur J Endocrinol* 151:463–465
- Alsaleem M, Saadeh L, Misra A, Madani S (2016) Neonatal isolated ACTH deficiency (IAD): a potentially life-threatening but treatable cause of neonatal cholestasis. *BMC Case Rep*. <https://doi.org/10.1136/bcr-2016-215032>
- Unal E, Yıldırım R, Taş FF, Tekin S, Sen A, Haspolat YK (2018) A rare cause of neonatal hypoglycemia in two siblings: *TBX19* gene mutation. *Hormones (Athens)* 17:269–273
- Akcan N, Serakıncı N, Turkgenç B, Bundak R, Bahceciler N, Temel SG (2017) A novel *TBX19* gene mutation in a case of congenital isolated adrenocorticotropin hormone deficiency presenting with recurrent respiratory tract infections. *Front Endocrinol (Lausanne)* 8:64
- Pulichino AM, Vallette-Kasic S, Couture C et al (2003a) Human and mouse TPIT gene mutations cause early-onset pituitary ACTH deficiency. *Genes Dev* 17:711–716
- Zachmann M, Girard J, Duc G, Illiq R, Prader A (1979) Low estradiol during pregnancy caused by isolated ACTH-deficiency. *Acta Paediatr Scand Suppl* 277:26–31
- Malpuech G, Vanlieféringhen P, Dechelotte P, Gaulme J, Labbe A, Guiot F (1988) Isolated familial adrenocorticotropin deficiency: prenatal diagnosis by maternal plasma estradiol assay. *Am J Med Genet* 29:125–130
- Weintrob N, Drouin J, Vallette-Kasic J et al (2006) Low estradiol levels in the maternal triple-marker screen as a predictor of isolated adrenocorticotropin hormone deficiency caused by a new mutation in the TPIT gene. *Pediatrics* 117:322–327
- Novoselova TV, Chan LF, Clark AJL (2018) Pathophysiology of melanocortin receptors and their accessory proteins. *Best Pract Res Clin Endocrinol Metab* 32:93–106
- Fridmanis D, Roga A, Klovins J (2017) ACTH receptor (MC2R) specificity: what do we know about underlying molecular mechanisms? *Front Endocrinol (Lausanne)* 8:13
- Naville D, Weber A, Genin E, Durand P, Clark AJ, Begeot M (1998) Exclusion of the adrenocorticotropin (ACTH) receptor (MC2R) locus in some families with ACTH resistance but no mutations of the MC2R coding sequence (familial glucocorticoid deficiency type 2). *J Clin Endocrinol Metab* 83:3592–3596
- Yeh JK, Evans JF, Niu QT, Aloia JF (2006) A possible role for melanocortin peptides in longitudinal growth. *J Endocrinol* 191: 677–686
- Chida D, Nakagawa S, Nagai S et al (2007) Melanocortin 2 receptor is required for adrenal gland development, steroidogenesis, and neonatal gluconeogenesis. *Proc Natl Acad Sci U S A* 104:18205–18210

24. Chung TT, Chan LF, Metherell LA, Clark AJ (2010) Phenotypic characteristics of familial glucocorticoid deficiency (FGD) type 1 and 2. *Clin Endocrinol* 72:589–594
25. Anisimova AS, Rubtsov PM, Akulich KA, Dmitriev SE, Frolova E, Tiulpakov A (2017) Late diagnosis of POMC deficiency and in vitro evidence of residual translation from allele with c.-11C>a mutation. *J Clin Endocrinol Metab* 102:359–362
26. Darcan S, Can S, Goksen D, Asar G (2010) Transient salt wasting in POMC-deficiency due to infection induced stress. *Exp Clin Endocrinol Diabetes* 118:281–283
27. Özen S, Özcan N, Uçar SK, Gökşen D, Darcan Ş (2015) Unexpected clinical features in a female patient with proopiomelanocortin (POMC) deficiency. *J Pediatr Endocrinol Metab* 28:691–694
28. Aslan IR, Ranadive SA, Valle I, Kollipara S, Noble JA, Vaisse C (2014) The melanocortin system and insulin resistance in humans: insights from a patient with complete POMC deficiency and type 1 diabetes mellitus. *Int J Obes* 38:148–151
29. Ozsu E, Bahm A (2017) Delayed diagnosis of proopiomelanocortin (POMC) deficiency with type 1 diabetes in a 9-year-old girl and her infant sibling. *J Pediatr Endocrinol Metab* 30:1137–1140