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Case Report

Long-Term Follow-up of a Case with TBX19 Mutation, a Rare Cause of Isolated ACTH Deficiency and Literature Review

Ceran et al. TBX19 Mutation: Long-Term Follow-up and Literature Review

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What is already known on this topic?
Variants in the *TBX19* are a rare cause of congenital isolated ACTH deficiency, presenting with hypoglycemia, seizures, and potentially fatal outcomes in the neonatal period. Early diagnosis and hydrocortisone replacement therapy are critical for survival and preventing long-term sequelae.

What this study adds?
This study presents long-term follow-up data from a patient with *TBX19* variants, who reached adulthood with normal physical and mental development. It highlights the importance of early and sustained hydrocortisone therapy.

Abstract
TPIT is a transcription factor required for *POMC* gene expression and pituitary corticotroph cell differentiation and is encoded by *TBX19*. Variants in *TBX19* cause early onset congenital isolated ACTH insufficiency with a mortality rate of up to 25% in the neonatal period. Mild dysmorphic findings may accompany some cases. Here, we report a case of isolated ACTH deficiency due to a *TBX19* variant diagnosed in the neonatal period, which was followed up until adulthood. The patient with hypoglycemia and convulsions on the first day of life were evaluated for hypocortisolemia and low ACTH. While neonatal cholestasis and hyperbilirubinemia were prominent, facial dysmorphism was unremarkable. He was diagnosed with isolated ACTH deficiency, and hydrocortisone replacement therapy was initiated. *TBX19* analysis revealed NM 005149 c.512T>C (p.Ile171Thr). Epileptic seizures were observed and antiepileptic treatment was initiated. Cranial MRI revealed an arachnoid cyst, cortical atrophy, and gliotic changes. The patient, which was also included in the first case report describing the gene encoding *TPIT*, reached the final height. He was 22 years old at the last follow-up, and his physical and mental development was normal. Neuromotor development and growth were normal. *TBX19* variants present with hypoglycemic convulsions in the early hours of the neonatal period and may lead to life-threatening neonatal death. Early hydrocortisone replacement therapy is significant for survival without sequelae. Continuing to monitor patients for long-term issues and additional discoveries could be beneficial for elucidating the genotype-phenotype correlation.
Keywords: Isolated ACTH deficiency, TBX19, TPIT

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Introduction
The T-box factor 19 (*TBX19*) (1q24.2) encodes the T-box pituitary restricted transcription factor (TPIT), a transcription factor specific for POMC-expressing cells in the mouse and human pituitary. TPIT is required for *POMC* transcription and terminal differentiation of pituitary corticotroph cells. Patients with variants in *TBX19* present in the first days of life with findings including hypoglycemic convulsion and cholestasis due to isolated ACTH deficiency (1). It is an important cause of early-onset congenital isolated ACTH deficiency, with a mortality rate of up to 25% in infancy (2).
Long-term follow-up findings of rare diseases are significant. Here, a patient who presented with hypoglycemia and convulsions in the first hours of life were diagnosed with isolated ACTH deficiency, variant in *TBX19* was detected on genetic examination. We share a 22-year follow-up from neonatal to adulthood to contribute to the literature.

Cases Presentation
A male baby, delivered via elective cesarean section at 38 weeks gestation, weighed 3400 grams, born to a 40-year-old mother, G4P4Y4, presented with cyanosis and hypoglycemia within the 3rd hour postnatally, necessitating intensive care unit monitoring. By the 5th day of life, the infant was referred to our clinic due to persistent hypoglycemia and cholestatic jaundice. Weight:3470 g, height: 52 cm, head circumference: 34 cm, anterior fontanel: 3x2 cm and posterior fontanel was closed. A flat nasal bridge, antimongoloid slant of the eyes, and a short, broad neck were observed (Figure 1). Clinical examination revealed various features, including decreased reflexes and hypotonia. Other system findings were normal; testicles were in the scrotum, and micropenis was not detected. In his family history, his parents were cousins (Table 1). Laboratory evaluations were as follows: blood glucose: 16 mg/dl, Na: 138 mmol/L, K: 5.1 mmol/L, total bilirubin: 17 mg/dl, direct bilirubin: 3.2 mg/dl, GGT: 293 U/L (0-55), ALP: 240 U/L (77-237), ALT: 21 U/L, AST: 45 U/L. Low blood glucose levels, and abnormal liver function tests were noted. Further investigation indicated isolated ACTH deficiency: peak cortisol response was inadequate with 10 mcg/dl in the low-dose ACTH stimulation test. Other anterior pituitary hormones were normal (Table 2). In the patient with ketotic hypoglycemia and cholestatic jaundice, isolated ACTH deficiency was found, and hydrocortisone treatment was started at a dose of 20 mg/m2/day. Genetic analysis revealed a homozygous missense variant (NM_005149 c.512T>C (p.Ile171Thr) in the *TBX19*. On follow-up, the patient's hydrocortisone dosage was adjusted. The patient had an afebrile seizure for the first time at the age of 15 months (concurrent blood glucose: 50 mg/dl). Further investigations revealed an arachnoid cyst, cortical atrophy, and contusional gliotic changes on cranial MRI. Pituitary size and electroencephalography were

normal. Diastasis recti and pectus excavatum were determined at the age of three years. Antiepileptic drug (topiramate) treatment was started at the age of 7.5 years upon the recommendation of the neurology department because epileptic attacks continued without hypoglycemia and in afebrile periods. At the age of 10.8 years, with a height of 140 cm (0.52 SD) and a body weight of 34 kg (1.5 SD), testicular volume was found to be 4 ml bilaterally, and the onset of puberty was determined. Pubic hair growth started at the age of 11.5 years, pubertal progression was normal, and puberty was completed by the age of 15 years. Antiepileptic treatment of the patient who had difficulty in controlling epileptic attacks and had seizures 2-3 times a year was continued with levetiracetam after the age of 16. He was still on 10 mg/m2 hydrocortisone and levetirasetame. Our patient, who was one of the first 8 cases involved in identifying the *TBX19* (TPIT). At the latest follow-up, now 22 years old, the patient remains asymptomatic, with stable clinical and laboratory parameters. On physical examination, body weight was 60 kg (BMI: 19 kg/m2), height was 175 cm (-0.25 SDS), and appropriate with the target height, the pubertal examination was Tanner stage 5. Notably, the patient exhibited normal pubertal development and overall well-being. He has had no seizures for the last 4 years on levetirasetame. He was on hydrocortisone 8 mg/m2/day with stable laboratory evaluations. Other pituitary hormones were normal. He continues to receive hydrocortisone and antiepileptic treatment, leading a productive life with satisfactory social integration.

Molecular analyses

Genetic testing at Laboratoire de Genetique Moleculaire, Glaxo Wellcome, Institut de Recherches Cliniques de Montreal, Canada, focused on sequencing the *TPIT* gene coding exons in the case and family members. All eight exons of the *TPIT* gene were amplified from genomic DNA, and PCR products were sequenced using a CEQ 2000 sequencer (Beckman-Coulter). The infant was homozygous for a missense mutation (I171T) in *TPIT*, affecting an amino acid in the T box. Family member DNA analysis revealed they were all heterozygous carriers of the mutation but unaffected (1,4).

Discussion:

Congenital isolated ACTH deficiency is a rare condition, although its frequency is unknown. It is generally divided into early (neonatal) and late (juvenile) onset according to the age of onset (3). The most common cause of isolated ACTH deficiencies observed mainly in the neonatal period, is autosomal recessive loss-of-function variants in *TBX19*. *TBX19* variants have been reported in approximately 100 cases in the literature. At least 45 different variants have been detected in these cases. Similar to the case presented here, most cases are diagnosed during the neonatal or infancy periods (1-12). In a study by Couture et al. which included 91 cases of congenital isolated ACTH deficiency, TBX19 variants were identified in 65% of cases with neonatal onset and complete ACTH deficiency. No variants were found in cases of partial or juvenile-onset ACTH deficiency (2).

The study published by Pulichino et al. (1) in 2004, including our case, was the first study to describe that autosomal recessive TPIT (*TBX19*) variants cause isolated adrenal insufficiency.

In the study of 17 patients with isolated adrenal insufficiency, 11 with neonatal onset, and 6 with late-onset (between 3.5-16 years of age), 7 different *TBX19* variants were in 8 (73%) of 11 patients with early onset. It was reported that all of these patients were diagnosed with hypoglycemia in the neonatal period; 3 of them also had cholestatic jaundice, 7 of them had a history of consanguineous marriage, and 4 of them had a history of sibling or relative death. In patients exhibiting low ACTH and markedly low cortisol levels during laboratory evaluations, a single-dose ACTH stimulation test failed to elicit an adequate cortisol response. However, following repeated ACTH injections, two patients demonstrated a sufficient cortisol response, suggesting the potential for adrenal function recovery in these individuals. There was no response to single or repeated CRH injections. No variant was detected in any of the late-onset patients. Interestingly, no variants were detected in late-onset cases, which is a key distinction.

Further supporting the early findings, Valette-Kasic et al. (5) published a study, adding 27 patients from 21 families to the body of knowledge on neonatal isolated adrenal insufficiency (1,4). They reported ten different TBX19 variants in 17 patients, reinforcing the role of TBX19 as the primary molecular cause of neonatal isolated adrenal insufficiency. Moreover, the study suggested that compound heterozygosity (5/17) may be more common than previously recognized, which points to a potential higher frequency of carriers in the general population. In some patients with no variant detected in the coding regions, mutations in the promoter or enhancer regions of TBX19 were suspected to affect gene expression and should be considered in patients with negative coding-region findings (5).

Our patient was diagnosed in the neonatal period and initiated on hydrocortisone treatment promptly, which is consistent with the recommended approach in the literature. Other reports of TBX19-related cases have described a variety of neurological and developmental sequelae. For instance, in a report by Peng et al., a patient diagnosed at 5 years of age after his infant sibling's diagnosis presented with subdural hematoma, epilepsy, and developmental delays (6). In contrast, Ünal et al. described two siblings diagnosed at different ages, with the younger sibling on earlier treatment and experiencing normal development (7). Similarly, Kardelen et al. found varying neurodevelopmental outcomes in their patients based on the timing of diagnosis and treatment (8). These findings underscore the importance of early diagnosis.

Other central nervous system (CNS)-related findings found in different cases include Arnold Chiari type 1 malformation, hypoplastic anterior pituitary, and transient growth hormone deficiency (in a patient whose hypoglycemia persisted despite hydrocortisone treatment) (5,8). Delayed age at diagnosis and previous hypoglycemias due to inadequate or irregular treatment may lead to permanent CNS damage. Although *TBX19* variants frequently present with findings such as hypoglycemia and cholestasis in the neonatal period, as in our cases, it should be taken into consideration that there may be cases that have not been diagnosed until late ages (13,14). Akcan et al. found low levels of ACTH and cortisol in a 7-year-old patient who had previously presented with recurrent respiratory tract infections and whose analysis performed for recurrent wizing were normal, and a diagnosis of isolated ACTH deficiency was made with further investigations. It was reported that a new variant was found in *TBX19* in this patient. It was recommended that adrenal function evaluation should be considered in recurrent respiratory tract infections in which the cause could not be found to not delay the diagnosis (13).

Another finding that may be helpful in early diagnosis may be low estradiol level detected during pregnancy was suggested in the study by Weintrob et al. In this study, low estriol was detected in the antenatal triple screening test of a patient who showed hypoglycemia since the neonatal period and died at the age of 7 weeks. In the subsequent pregnancy of the mother of the patient, low estriol was detected again in the screening test, and X-linked ichthyosis and Smith-Lemli-Opitz syndromes were excluded. Postnatal basal and stimulated cortisol and ACTH levels were examined isolated ACTH deficiency was diagnosed, and early treatment was started. A genetic examination of the patient revealed a pathogenic variant in *TBX19* encoding TPIT (9).

In the literature, findings including short stature, tall stature, puberty precocity, osteoporosis, congenital cardiopathy, bicuspid aorta, microcephaly, scaphocephaly, and atypical facial appearance have been reported in cases with isolated ACTH deficiency with *TBX19* variant (5,8,10,15,16). However, the relationship between these dysmorphic features and specific TBX19 variants remains unclear. Our patient, for example, exhibited only mild dysmorphic features. A phenotype-genotype relationship has not yet been established in *TBX19* variants. Kardelen et al.(8) reported a patient with a different variant (NM_005149.2:c.584C>T (p.Thr195Ile), flat nasal bridge, oblique and antimongoloid eyes, epicanthus and strabismus (8). The variant was found in two sibling cases reported by Ünal et al. c.856 C>T (p.Arg286Ter). Facial dysmorphism was not defined in these patients who presented with hypoglycemia in the neonatal period (7). In the case presented by Weijing et al.,

hypertelorism, narrow palpebral fissures, and abnormally low ears were reported, which were more similar to our patient's. Two novel heterozygous variants (c.205C>T (p.R69W) and large deletion in exon 2) were found in this case (15). Although more cases need to be defined to make a genotype-phenotype correlation for these patients carrying different variants in the *TBX19*, we think that a good description of the dysmorphic findings, if any, in the cases may provide a clue.

In the case report by Abalı et al., a 4-year and 8-month-old female patient was diagnosed for the first time at the age of 3 years after hypoglycemic convulsions. In the follow-up of the patient who had a tall stature (2.2 SDS) at presentation, it was reported that premature telarche started at the age of 5 years and central puberty started at the age of 7 years. Since rapid progression was not observed in the follow-up, no treatment was given for early puberty. Since it is known that glucocorticoids have a negative inhibition on IGFBP5, in this patient, it was hypothesized that glucocorticoid deficiency and the lack of inhibition might be one reason explaining the height (16). Although TPIT is known to have a suppressive effect on the differentiation of gonadotrope cells, Valette Kasic et al. reported that they did not observe puberty precocity in any of their patients (5). In the follow-up of our case, the growth rate was in the normal range, and puberty started on time, progressed at a normal rate, and reached the final height. In this case, the final height was compatible with the target height.

ACTH is known to be essential for the development and maintenance of the adrenal gland and adrenarche. In the literature, cases carrying *TBX19* variant and not showing adrenarche have been described. Valette-Kasic et al. found aldosterone and DHEAS levels in the normal range in 3 cases without adrenarche (5). Kardelen et al. presented a 14-year-old patient in whom adrenal imaging was normal, but adrenarche did not develop, and DHEAS levels were low (8). In our case, adrenarche development was normal. Anthropometric and puberty follow-up is ongoing. Since our case is one of the first cases described in the literature, it may also be the case with the longest follow-up. A clear relationship between *TBX19* variants and growth or the pituitary-gonadal axis has not yet been defined, and long-term follow-up of more cases is needed in this respect.

In conclusion, the evaluation of adrenal function in neonates and infants presenting with hypoglycemia, particularly in cases with concomitant conditions such as cholestasis, is critical for early diagnosis and management. *TBX19* gene variants represent the most common molecular cause of isolated ACTH deficiency with neonatal onset and may present with severe manifestations, including hypoglycemic seizures in the early neonatal period, which can lead to life-threatening outcomes if left untreated. Early recognition and prompt initiation of hydrocortisone replacement therapy are crucial for improving survival and preventing long-term complications. It is important to document and describe any dysmorphic features in detail, as these may provide valuable clues for diagnosis. Furthermore, long-term follow-up of the patients, focusing on potential future health issues and additional findings, is essential for further elucidating the genotype-phenotype correlation and improving management strategies.

Statements

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Statement of Ethics

Written informed consent was obtained from the patient and parents for publication of this case report.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Author Contributions

Medical Practices:AC, SC, ZA, ZS, EO , Concept: ZA, ZS, EO, MB, Design: ZA, ZS, MB, Data collection: AC,SC, ZA, ZS, EO , Analysis: : AC, ZA, ZS, EO, MB, Literature Search: SC, AC, ZS,ZA,EO MB , Writing: AC,SC, ZA, ZS, EO, MB

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Table 1. Clinical Characteristics of the Case

	Case 1
Birth Week	38
Birth Weight, gr(SDS)	3400
Gender	M
Consanguinity	present
Family history of neonatal infant death	none
Mother height, cm (SDS)	165 (0.32)
Father height, cm (SDS)	168 (-1.3)
Target height, cm (SDS)	173 (-0.52)
Time of onset of symptoms	First day of life
Admission	
Complaint on admission	Persistent hypoglycemia. cholestatic jaundice, convulsions
Age of admission	5 days
Age at diagnosis	newborn
Height, cm (SDS)	52 (0.59)
Body Weight (grams)	3470
Head circumference, cm (SDS)	34 (-1)
Additional findings	Diastasis recti, pectus excavatum
Final Examination	
Age, decimal(years)	22
Height, cm (SDS)	175 (-0.19)
Body Weight, kg (SDS)	60 (-1.34)
BMI (SDS)	19 (-1.47)
Tanner Stage	5
Additional findings	Epilepsy
SDS: Standard Deviation Score, BMI: Body Mass Index	

Table 2. Laboratory and Imaging Characteristics of the Case

	Case
Admission	
Glucose, mg/dl	16
Na/K, mmol/l	138/5.1
ACTH, pg/ml (5-50)	< 5
Basal cortisol, µg/dl	0.1
Peak cortisol response to low-dose ACTH stimulation test, µg/dl	10
Ketone (in urine)	++
Growth Hormone, ng/ml	8,5
LH/FSH, µIU/ml	3.6/0.83
Total testosterone, ng/dl	74,5
Prolactin, ng/ml (1.9-25)	20
TSH, µIU/ml (0,5-5)	4.4
sT4, pmol/L	11.3 (N: 10-28)
Pituitary & Cranial MRI	Arachnoid cyst, cortical atrophy, contusional gliotic changes. Normal pituitary gland.

MRI of the abdomen	-
Molecular Analysis	I171T homozygous missense variant in exon 3 of TPIT(*TBX19*)
Final Examination	
Glucose, mg/dl	83
Na/K, mmol/l	141/4
TSH, µIU/ml	4.3
sT4, pmol/L	12.3 (N: 7-16)
Na, sodium; K, potassium ACTH, adrenocorticotropic hormone	sT4, free thyroxine TSH, thyroid stimulating hormone

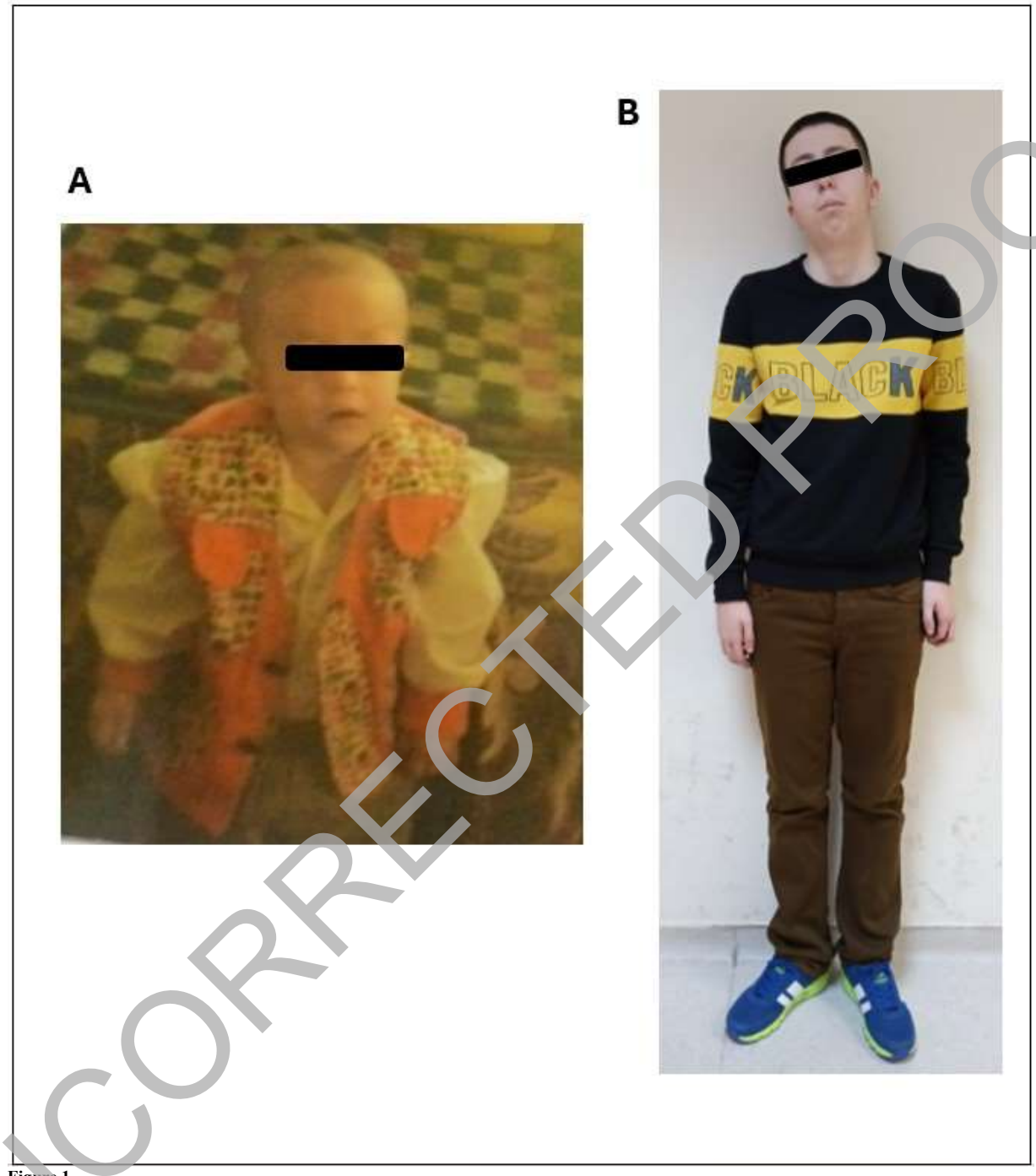

Figure 1.

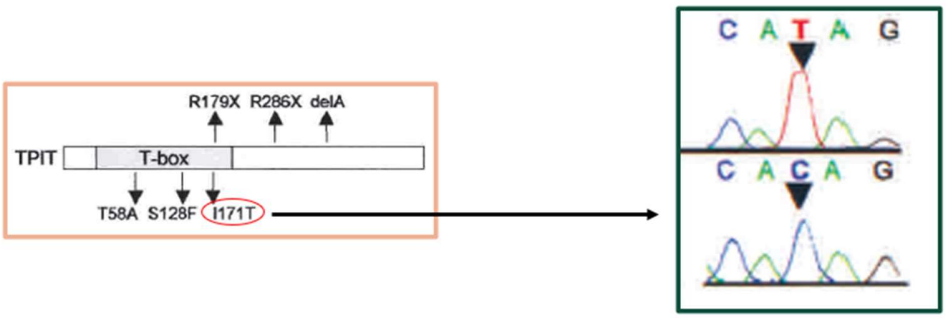

Figure 2. A homozygous mutation, c.512T>C (p.Ile171Thr), was detected in the patient. The parents were heterozygous (1)