DOI: 10.4274/jcrpe.galenos.2025.2025-6-7

Case Report

A Novel *THRβ* Variant in a Child With Resistance to Thyroid Hormone β: Diagnostic and Therapeutic Challenges

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What is already known on this topic?
Resistance to thyroid hormone beta (RTHβ) is a rare genetic disorder typically caused by mutations in the *THRB* gene. Patients may present with elevated thyroid hormone levels and non-suppressed TSH, often mimicking TSH-secreting pituitary adenomas. Genetic confirmation is essential for accurate diagnosis and to avoid unnecessary interventions.

What this study adds?
This study presents a pediatric case of RTHβ associated with a previously unreported likely pathogenic *THRB* variant (p.Phe459Ser), affecting a highly conserved amino acid within a known mutational hotspot.This report expands the current mutation spectrum of *THRB* and reinforces the diagnostic utility of early genetic testing in distinguishing RTHβ from TSHoma.

Abstract
Resistance to thyroid hormone beta (RTHβ) is a rare condition typically caused by mutations in the THRβ gene, characterized by elevated thyroid hormones with non-suppressed TSH levels. We present a pediatric case of RTHβ associated with a novel *THRβ* variant, emphasizing diagnostic challenges and the importance of individualized treatment. A 6.5-year-old girl was evaluated for learning difficulties and tachycardia. Laboratory findings showed elevated free T3 and T4 with non-suppressed TSH. Pituitary MRI showed a 5x6 mm lesion, raising suspicion for TSHoma. Genetic testing of the *THRβ* gene was performed. A novel heterozygous *THRβ* variant (c.1376T>C; p.Phe459Ser) was identified in both the patient and her father. The mutation affects a highly conserved residue within the ligand-binding domain. Clinical and biochemical findings were consistent with RTHβ. Atenolol therapy was initiated to manage tachycardia with favorable response.This case highlights the potential for misdiagnosis of RTHβ as TSHoma and underscores the value of genetic testing in differentiating the two. The identification of a novel variant at codon 459 expands the mutational spectrum of *THRβ* and supports its role as a hotspot region relevant to RTHβ pathogenesis.
Keywords: Thyroid hormone resistance, THRB mutation, TSHoma

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15.06.2025
08.09.2025

Epub: 17.09.2025

Introduction

Thyroid hormone resistance (RTH) is a rare autosomal dominant disorder characterized by impaired sensitivity of target tissues to circulating thyroid hormones, leading to elevated serum levels of T3 and T4 with an inappropriately non-suppressed or normal TSH due to reduced feedback inhibition at the pituitary level (1). RTH was first described in 1967 and is estimated to affect approximately 1 in 40,000–50,000 live births (2). Approximately 75% of RTH cases are caused by identifiable genetic mutations, most commonly affecting the *THRβ* gene. Thyroid hormone receptors (TRs) belong to the NR1 subfamily of the nuclear receptor (NR) superfamily, which also includes receptors such as retinoic acid receptor (RAR), vitamin D receptor (VDR), peroxisome proliferator-activated receptor (PPAR), and liver X receptor (LXR) (3). The *THRβ* gene encodes the β isoform of the thyroid hormone receptor, and mutations in this gene are known to impair receptor function. The mutant receptor exerts a dominant negative effect on the wild-type receptor, interfering with normal thyroid hormone signaling and cellular response.

Clinical presentations are highly variable, ranging from asymptomatic individuals to those showing signs of thyroid hormone deficiency such as delayed growth or cognitive dysfunction, or symptoms resembling thyrotoxicosis, including tachycardia, advanced bone age, or hyperactivity (4–6). In patients with RTH, target tissue responses to elevated thyroid hormone levels may differ across organ systems. While some tissues exhibit signs of hyperthyroidism, such as tachycardia, others may present features of hypothyroidism, including fatigue or growth delay. Goiter and sinus tachycardia are among the most commonly reported clinical signs (7,8).

Case: The patient was a 6.5-year-old girl referred to our pediatric endocrinology clinic due to elevated thyroid hormone levels detected during evaluation for learning difficulties. Given the inappropriate TSH secretion despite elevated thyroid hormone levels, a pituitary MRI was obtained to rule out a TSH-secreting adenoma (TSHoma). A mildly hyperintense nodule measuring approximately 5 × 6 mm was observed in the right posterior portion of the pituitary gland on T1-weighted axial sequences. Her past medical history revealed normal birth weight (2750 g), sitting at 6 months and walking at 18 months. There was no history of neonatal hypothyroidism screening abnormalities. Family reported long-standing attention deficit, learning difficulties, and mild intellectual disability. On admission, her weight was 19 kg (−0.91 SDS), height 122 cm (0.78 SDS), blood pressure 120/60 mmHg (sys:above 99 per dia:50-90 per), and heart rate 115 bpm. She was in prepubertal Tanner stage I. On physical examination, she exhibited subtle dysmorphic features, including a bird-like facial features and a mildly protruding sternum consistent with pigeon chest. Laboratory evaluation revealed significantly elevated levels of thyroid hormones with an inappropriately normal TSH, consistent with a biochemical profile suggestive of thyroid hormone resistance. Serum thyroid-stimulating hormone (TSH) was 2.80 mIU/L (reference: 0.67–4.16), free thyroxine (FT4) was markedly elevated at 46.8 ng/L (reference: 10.4–16.4), and free triiodothyronine (FT3) was also elevated at 16.6 ng/L (reference: 3.3–4.8). Thyroid autoimmunity was excluded, as anti-

thyroid peroxidase antibodies (anti-TPO) and anti-thyroglobulin antibodies (anti-Tg) were negative. TSH receptor antibodies (TRAb) were within the normal range at 0.43 IU/L (reference: <1.5). Lipid profile, renal and liver function tests were normal. SHBG was within normal limits at 78.6 nmol/L (18–144). Thyroid ultrasound demonstrated mild enlargement of both lobes with a total volume of 5.72 mL (+3.12 SDS), consistent with diffuse goiter. No nodules or lymphadenopathy were observed. Cardiac assessment showed sinus tachycardia on electrocardiogram and mildly elevated blood pressure. Echocardiography revealed no structural heart abnormalities. Given the biochemical pattern of elevated thyroid hormones with an inappropriately normal TSH, and the absence of autoimmune thyroid disease or thyroid nodules, resistance to thyroid hormone (RTH) was suspected. Family screening was initiated. Thyroid function tests were performed for the patient's parents, as well as her brother and sister, and the results for the siblings and mother were within normal limits (Table 1). Her father's thyroid function tests also showed elevated FT3 and FT4 with mildly elevated TSH (TSH: 5.98 µIU/mL (0,3-4,2), FT4: 3.73 ng/dL (0,8-1,8), FT3: 12.8 ng/dL(2,3-4,4)), raising suspicion for familial RTH. According to family members, he had a history suggestive of psychological distress, and we also learned that he had behavioral problems, although a formal psychiatric evaluation had not been performed. He was unemployed and exhibited social withdrawal. He spent most of his time at home and had limited engagement in daily activities. No apparent dysmorphic features were observed on physical examination. *THRβ* gene (NM_001354712.2) was analyzed using next-generation sequencing (NGS). A heterozygous variant in the *THRβ* gene was identified in the patient. The patient was started on atenolol due to persistent sinus tachycardia. Propranolol was avoided because of its effect on peripheral conversion of T4 to T3. Atenolol was well tolerated, with clinical improvement in heart rate and subjective symptoms.

Genomic DNA analysis

Informed consent for the molecular studies was obtained from all family members. The coding exons 4, 5, 6, 7, 9, 10, and 11 of the *THRβ* gene(NM_001354712.2) were analyzed using next-generation sequencing (NGS). Both exonic sequences and exon-intron boundaries were evaluated. A heterozygous mutation at codon 459 (c.1376T>C), located in exon 11 of the *THRβ* gene, was identified, resulting in the substitution of phenylalanine with serine (p.Phe459Ser).

Both parents underwent Sanger sequencing, which revealed that the variant was paternally inherited (Fig 1). As previously described, the father's thyroid function tests demonstrated a biochemical pattern consistent with thyroid hormone resistance. The mother tested negative for the variant and had normal thyroid function. The substitution of phenylalanine, an aromatic and hydrophobic amino acid, with serine, a smaller, hydrophilic polar amino acid, may disrupt the three-dimensional structure of the protein and potentially impair the function of critical domains (Fig 2).

Discussion

Thyroid hormone receptors (TRs) are classified into four principal isoforms: TRα1, TRα2, TRβ1, and TRβ2. Among these, TRβ1 is mainly found in the brain, liver, and kidneys, whereas TRβ2 is largely confined to the hypothalamus and pituitary gland (9). This distinct pattern of tissue expression plays an important role in the wide variability of clinical features seen in resistance to thyroid hormone beta (RTHβ). Individuals carrying pathogenic *THRβ* variants most frequently present with goiter, palpitations, reduced growth velocity, and developmental delays (10). In addition, dysmorphic features—including bird-like facial characteristics and a pigeon-shaped chest—have also been reported, consistent with the physical findings in our patient (11).

In our case, the patient was initially referred with external MRI findings that described a small nodular lesion in the posterior region of the pituitary gland, raising the possibility of a TSH-secreting pituitary adenoma (12). This differential diagnosis is clinically relevant, as both TSHoma and RTH present with elevated thyroid hormones and inappropriately normal or elevated TSH levels (12,13). This overlap may lead to misdiagnosis and, in some cases, unnecessary interventions. In a case reported by Karaköse et al., a patient carrying a pathogenic His435Arg variant in the *THRβ* gene was initially misdiagnosed with a TSHoma based on pituitary MRI findings and underwent an unnecessary adenomectomy. Genetic testing later confirmed the diagnosis of RTHβ, and retrospective evaluation of clinical features supported this diagnosis rather than a functional pituitary tumor (14).

Similarly, our patient was referred due to elevated thyroid hormones and non-suppressed TSH, with a pituitary MRI revealing a 5x6 mm nodule in the posterior pituitary. However, the absence of additional pituitary hormone abnormalities, the lack of progressive mass effect, and the identification of the same *THRβ* gene mutation in her father supported the diagnosis of familial RTHβ over TSHoma. This case underscores the importance of incorporating genetic testing early in the diagnostic workup to avoid misdiagnosis and overtreatment. Moreover, it highlights the need for clinical correlation beyond imaging findings**,** as small non-functional pituitary incidentalomas are not uncommon in the general pediatric population.

The management of RTH primarily focuses on alleviating clinical symptoms rather than normalizing circulating thyroid hormone (TH) levels. In many cases, the elevated levels of TH provide sufficient compensation for tissue resistance, making pharmacological intervention unnecessary. In instances where hypothyroid symptoms are evident particularly in infants prompt initiation of exogenous thyroid hormone replacement is essential, with levothyroxine serving as the treatment of choice (15). Patients who present with symptoms of hyperthyroidism may benefit from symptomatic relief using β-adrenergic blockers or anxiolytic medications, depending on the nature and severity of their complaints.

For individuals with persistently elevated TSH levels, triiodothyroacetic acid (TRIAC), a synthetic analog of T3, can be administered to suppress TSH secretion. This not only helps reduce goiter size but also lowers circulating TH levels and may decrease the risk of developing thyroid nodules, thyroid cancer, or autoimmune thyroid diseases (16,17). In our patient, the primary clinical concern was persistent sinus tachycardia in the absence of overt thyrotoxic features. Based on current management recommendations and to address the patient's symptoms, atenolol was initiated. As a cardioselective β1-blocker, atenolol effectively reduced heart rate without interfering with peripheral thyroid hormone metabolism an advantage over non-selective agents such as propranolol, which inhibit the conversion of T4 to T3. The patient tolerated the medication well, with noticeable clinical improvement. This treatment decision is consistent with the broader therapeutic approach in RTH, which emphasizes personalized, symptom-driven management rather than aggressive correction of laboratory abnormalities.

Resistance to thyroid hormone is caused by mutations in the thyroid hormone receptor beta (*THRβ*) gene, which encodes the β isoform of the thyroid hormone receptor. The mutant receptor exerts a dominant negative effect on the wild-type receptor, resulting in impaired receptor function.

According to the Human Gene Mutation Database (HGMD), more than 180 disease-causing mutations have been identified in the *THRβ* gene. Over 85% of these are point mutations(missense and nonsense variants). Approximately 90% of the reported variants are located within the nuclear receptor ligand-binding domain (NR LBD), spanning codons 271 to 461. The variant identified in our patient is located near the C-terminal end of this critical domain, further supporting its potential pathogenic impact. To our knowledge, the *THRβ* variant identified in both the patient and her father has not been previously reported in major population databases or the literature. The variant was located within the region spanning amino acids 374 to 461, which has been previously reported as a mutational hot spot (18). It was not found in population databases including gnomAD, TOPMed Bravo, and GME Variome. Based on *in silico* predictions, the majority of algorithms classify this variant as deleterious(REVEL, AlphaMissense, DANN, MutationTaster, MetaLR). The variant is also located within a highly conserved region across vertebrate species(PhastCons:1.000, PhyloP:9.257). Multiple sequence alignment of orthologous TRβ sequences from 12 species revealed a highly conserved region encompassing the Phe459 residue (Table 2). The same amino acid change (p.Phe459Ser) has not been previously reported in the literature. However, other nucleotide substitutions affecting the same codon—c.1376T>G (p.Phe459Cys) and c.1377C>G (p.Phe459Leu) have been reported in both ClinVar, classified as pathogenic and likely

pathogenic respectively, and in the literature (19,20). In addition, p.Phe459Val substitution has been described in a Chinese patient presenting with short stature and delayed speech development, similar to our patient (21).
Therefore, this variant is classified as likely pathogenic according to the American College of Medical Genetics(ACMG) guidelines(PP2, PP3, PM1, PM2, PM5).
This case report is subject to several limitations. First, although the pathogenicity of the *THRB* variant was supported by in silico predictions and evolutionary conservation, no functional validation studies were performed. Second, neither dynamic pituitary testing, such as a TRH stimulation test, nor functional imaging was carried out to further characterize the pituitary lesion. These limitations may affect the depth of diagnostic interpretation and should be taken into account when evaluating the findings.
In conclusion, this case highlights the diagnostic complexity of resistance to thyroid hormone beta (RTHβ), especially when imaging findings suggest a TSH-secreting pituitary adenoma. The presence of a novel likely pathogenic *THRβ* variant (p.Phe459Ser) in both the patient and her father, along with the absence of other pituitary hormone abnormalities, supported the diagnosis of RTHβ. Our report emphasizes the importance of integrating clinical, biochemical, radiological, and genetic data to avoid misdiagnosis and unnecessary interventions. Furthermore, our identification of a previously unreported *THRβ* variant enriches the existing mutation spectrum and reinforces the functional significance of codon 459. In this case, using a selective β1-blocker based on the patient's symptoms helped improve her clinical condition.

Presentation: 29th National Congress of Pediatric Endocrinology and Diabetes, April 15–20, 2025, Cornelia Convention Center, Antalya, Turkey.

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Table 1. Thyroid function test results of the patient's parents and siblings.

	TSH (0,3-4,2) µIU/mL	**ST4** (0,8-1,8) ng/dL	**ST3 (**2,3-4,4) ng/dL
Father	**5,98**	**3,73**	**12,8**
Mother	**3,42**	**1,1**	**3,8**
Brother	**2,2**	**1,02**	**3,9**
Sister	**3,8**	**1,2**	**3,7**

Table 2. Alignment of orthologous sequences from 12 species using Clustal Omega

Homo sapiens	453 PLFLEV**F**ED 461
Felis catus	453 PLFLEV**F**ED 461
Oryctolagus cuniculus	468 PLFLEV**F**ED 476
Sus scrofa	468 PLFLEV**F**ED 476
Bos taurus	468 PLFLEV**F**ED 476
Capra hircus	468 PLFLEV**F**ED 476
Nomascus leucogenys	468 PLFLEV**F**ED 476
Macaca nemestrina	468 PLFLEV**F**ED 476
Callithrix jacchus	468 PLFLEV**F**ED 476
Pan troglodytes	468 PLFLEV**F**ED 476
Equus caballus	468 PLFLEV**F**ED 476

Ailuropoda melanoleuca 468 PLFLEV**F**ED 476

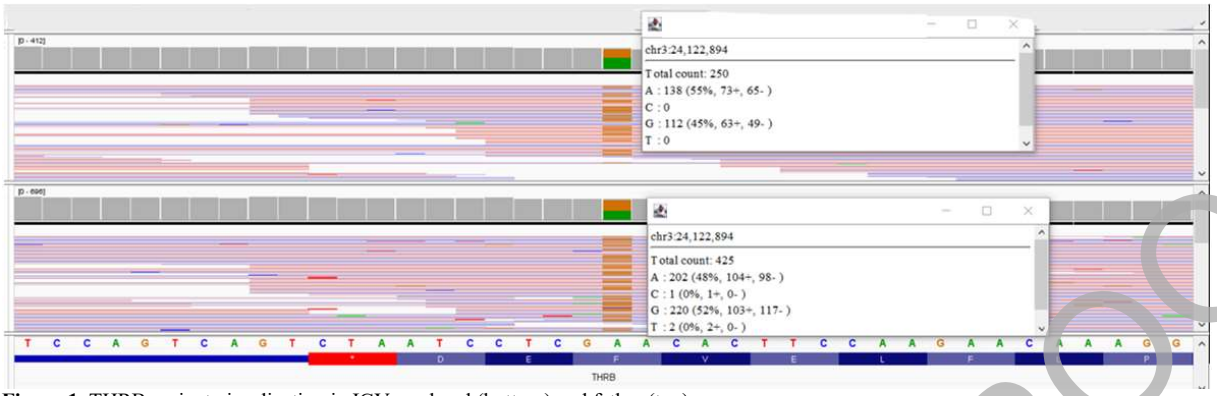

Figure 1. THRB variant visualization in IGV: proband (bottom) and father (top)

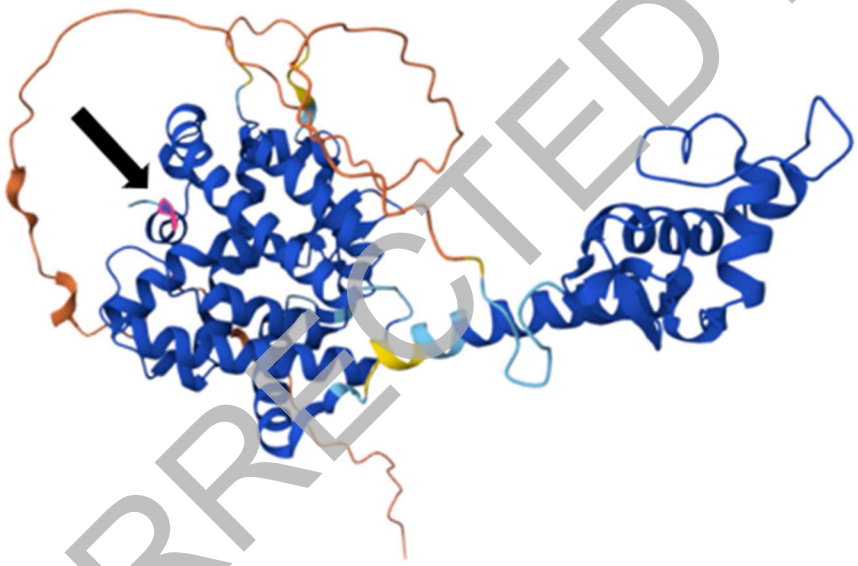

Figure 2. Crystal structure of the human *THRβ* gene, highlighting the location of the Phe459 residue (magenta), which is indicated by black arrow