

# Resistance to thyroid hormone $\beta$ (RTH $\beta$ ) due to a THRB mutation (p.Arg429Gln) in a 39-year-old woman initially treated for thyrotoxicosis

Riva EL Assaad

[riva.el.assaad@akademiska.se](mailto:riva.el.assaad@akademiska.se)

Uppsala University

Niklas Dahl

Uppsala University

Selwan Khamisi

Uppsala University

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## Case Report

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# Abstract

## Background

Resistance to thyroid hormone beta (RTH $\beta$ ) is a rare inherited disorder characterised by elevated free thyroid hormone levels with non-suppressed or elevated TSH, most commonly caused by mutations in the *THRB* gene. The biochemical profile often mimics thyrotoxicosis or a TSH secreting pituitary adenoma, contributing to delayed or inappropriate treatment.

## Methods

We describe the clinical course, biochemical findings and genetic analysis of a 39 year old woman who presented with palpitations, hypertension and elevated FT4 and FT3 despite a non-suppressed TSH, and who demonstrated no response to antithyroid medication. Genetic sequencing was performed.

## Results

Initial testing showed normal TSH levels (2.45 mU/L), and elevated FT4 (29 pmol/L) and FT3 (7.6 pmol/L). Antithyroid therapy (Thiamazole) led to a paradoxical rise in TSH. Pituitary MRI was normal. Genetic analysis identified a heterozygous *THRB* gene variant,

NM\_001354712.2:c.1286G>A (p.Arg429Gln), classified as pathogenic. Antithyroid therapy was discontinued, and management was transitioned to betablockade. The patient remained clinically stable at a 24-months follow-up, and genetic counselling was initiated.

## Conclusion

This case highlights that elevated FT4/FT3 with inappropriately normal or high TSH should raise suspicion of RTH $\beta$ . Genetic confirmation is critical to avoid unnecessary interventions and to guide appropriate long-term management and family screening.

# Introduction

Resistance to thyroid hormone beta (RTH $\beta$ ) is a rare endocrine syndrome caused by germline pathogenic variants in the *THRB* gene, encoding the thyroid hormone receptor  $\beta$  (TR $\beta$ ). In RTH $\beta$ , target tissues (including the pituitary) have reduced sensitivity to thyroid hormone, leading to elevated circulating free T4 (FT4) and free T3 (FT3) levels with an inappropriately normal or elevated TSH [1].

The biochemical profile in RTH $\beta$  overlaps with that of a TSH-secreting pituitary adenoma or assay interference and may therefore be misdiagnosed with inappropriate therapeutic interventions (e.g., antithyroid drugs, pituitary surgery) [1, 6–7].

Furthermore, RTH $\beta$  commonly coexists with autoimmune thyroid disease (AITD) that may confound interpretation of thyroid function tests by contributing to fluctuations of the typical

RTH $\beta$  pattern [2, 4–5].

Illustrative case reports include misdiagnosis of RTH $\beta$  for a pituitary tumor followed by unnecessary transsphenoidal surgery [3], and prolonged antithyroid therapy or thyroidectomy prior to recognizing hormone resistance [4, 7].

Early recognition of RTH $\beta$  by genetic analysis of *THRB* is therefore key to avoid unnecessary interventions and to guide family counselling [1–3, 6]. We present a case of

RTH $\beta$  in a 39-year-old woman with the *THRB* variant

(p.Arg429Gln), highlighting diagnostic pitfalls and management.

## Case presentation

A 39-year-old Caucasian female with no prior thyroid disorder or heredity for thyroid diseases presented in July 2023 with a six-month history of palpitations, fatigue and headaches. She worked retail part-time while studying, was a non-smoker and followed a balanced diet. Her obstetric history included gestational hypertension and pre-eclampsia, and diet-controlled gestational diabetes in her most recent pregnancy; otherwise, healthy. On examination blood pressure was 150/85 mmHg, heart rate 95–105 bpm; no goitre, ophthalmopathy or tremor were noted.

Initial laboratory results:

- TSH 2.45 mU/L (ref ~ 0.4–4.0)
- FT4 29 pmol/L (ref ~ 12–22)
- FT3 7.6 pmol/L (ref ~ 3.5–6.5)
- TPO-Ab and TRAb negative

Other investigations (CBC, renal, calcium, glucose, inflammatory markers) were unremarkable.

She was commenced on amlodipine for hypertension (5 mg → 10 mg) and metoprolol 50 mg daily for tachycardia.

## Further evaluation

Because TSH was not suppressed despite elevated FT4 and FT3, thyroid scintigraphy and pituitary work-up were initiated. Scintigraphy (August 2023) showed borderline increased uptake, raising mild suspicion of Graves' disease; however, antibodies remained negative.

Pituitary evaluation including MRI (November 2023) showed no adenoma. Despite symptomatic improvement with beta-blockade, biochemical abnormalities persisted.

# Diagnostic assessment

Between February and June 2024, thiamazole (initially 5 mg daily then up to 15 mg/day) was given without clinical or biochemical improvement; FT4 remained elevated and TSH paradoxically rose to 7.52 mU/L (Table 1). This paradox (antithyroid therapy causing TSH elevation) suggested thyroid hormone resistance rather than excess production.

Table 1  
Key laboratory values over time

| Date     | TSH<br>(mU/L) | FT4<br>(pmol/L) | FT3<br>(pmol/L) | Notes                     |
|----------|---------------|-----------------|-----------------|---------------------------|
| Jul 2023 | 2.45          | 29              | 7.6             | Initial presentation      |
| Jan 2024 | 2.46          | 28              | 8.4             | Follow up                 |
| Mar 2024 | 3.42          | 24              | 6.7             | On thiamazole             |
| Jun 2024 | 7.52          | 24              | 7.9             | Paradoxical TSH elevation |
| Jul 2024 | 11.00         | 19.4            | 6.4             | Increased thiamazole dose |
| Sep 2024 | 5.83          | 24              | 6.8             | Reduced thiamazole dose   |
| Jun 2025 | 1.95          | 30              | 7.1             | After levothyroxine trial |
| Sep 2025 | 2.19          | 33              | 8.6             | Stable on betablocker     |
| Dec 2025 | 2.16          | 30              | 7.6             | Stable on betablocker     |

Genetic testing performed later in November and results in January 2025 revealed a heterozygous *THRB* variant NM\_001354712.2:c.1286G > A (p.Arg429Gln). According to the accompanying genetic report, the variant is classified as pathogenic as it is found at extremely low frequency in the population (gnomAD v4.1.0: 1/161 401 alleles). *In silico* prediction of the variant (REVEL score 0.932–1) indicates a damaging effect, and functional studies have shown that it affects TRβ function (PMIDs: 8040303, 11167935, 15815068, 21703645, 35253369). Taken together, the diagnosis RTHβ could be established. The *THRB* variant causes autosomal dominant RTHβ and genetic counselling was recommended with possibilities for carrier screening of family members.

## Management & follow-up

Following diagnosis in January 2025, thiamazole was permanently stopped. Metoprolol was escalated to 100 mg daily with good symptomatic control of palpitations and heart rate (80–90 bpm). In March 2025, labs were TSH 4.95 mU/L, FT4 21 pmol/L, FT3 6.5 pmol/L. Given ongoing fatigue and mild hypothyroid-type symptoms, a trial of levothyroxine 25 µg daily was attempted, but no symptomatic benefit was noted; it was discontinued by June 2025

(labs: TSH 1.9 mU/L, FT4 30 pmol/L, FT3 7.1 pmol/L). By September 2025, TSH was 2.2 mU/L and the patient remained clinically stable with continued beta-blockade, lifestyle counselling (exercise, diet) and decline of GLP-1 agonist therapy for weight management. Bone density testing was done and showed normal results. Family genetic counselling has been initiated (Fig. 1).

## Discussion

The case illustrates the classical biochemical and clinical features of RTH $\beta$ : elevated FT4 and FT3 with inappropriately normal or elevated TSH, poor response (or paradoxical response) to antithyroid or thyroxine therapy, and normal pituitary imaging. The pathogenic *THRB* missense variant resulting in p.Arg429Gln variant identified in this patient affects a highly conserved residue in the ligand-binding domain of TR $\beta$ . Published functional studies demonstrate impaired T3 binding, reduced coactivator recruitment and decreased transcriptional activation of target genes. In particular, mutations affecting the Arg429 residue have been shown to disrupt ligand-dependent coactivator recruitment, supporting their pathogenicity [10]. Moreover, the amino acid substitution p.Arg429Gln has been reported in another patient with persistent hormone elevation and variable tissue responsiveness, consistent with our patient's presentation [9].

Key diagnostic lessons include:

- Always consider RTH $\beta$  in the differential when TSH is not suppressed despite elevated thyroid hormones.
- A normal pituitary MRI and negative pituitary hormone panel argue against a

TSH-secreting adenoma.

- Paradoxical laboratory responses to therapy (e.g., thionamide causing TSH increase) are strongly suggestive of RTH $\beta$ .
- Genetic testing for *THRB* mutations is vital for definitive diagnosis and avoids inappropriate interventions (e.g., unnecessary surgery or lifelong antithyroid therapy). Management of RTH $\beta$  is mainly symptomatic. As target tissues (such as the heart) may remain sensitive (via TR $\alpha$ ), symptoms such as tachycardia may be treated with beta-blockers. Antithyroid or thyroxine therapies are generally not effective and may destabilize hormone feedback. Genetic counselling is essential because of the autosomal dominant inheritance pattern.

## Limitations

Although we did not perform functional assays ourselves, the variant is well characterized in the literature. Family testing is underway but results are pending.

## Conclusion

In summary, we present a 39-year-old woman with RTH $\beta$  due to the *THRB* missense variant (p.Arg429Gln), initially managed as thyrotoxicosis. The case underscores the importance of recognizing the biochemical signature of RTH $\beta$ —elevated FT4/FT3 with an inappropriately normal or high TSH—as highlighted in current literature [1]. Early genetic testing is critical in patients with discordant thyroid function tests, as delays may lead to misdiagnosis and unnecessary treatments such as antithyroid medication, thyroidectomy or even pituitary surgery [2–4]. Accurate identification of underlying mechanisms to RTH $\beta$  helps clinicians avoid inappropriate interventions and supports appropriate long-term management, including family counselling. Increasing awareness of this rare condition will help reduce diagnostic errors and improve patient outcomes.

## Declarations

**Ethics and consent to participate:** Written informed consent obtained from the patient for participation.

**Consent to publish:** Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

**Availability of data and materials:** data and materials available in the patients records.

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**Authors contributions:** S.K has been the treating physician and prepared the case presentation, further evaluation and the diagnostic assessment.

N.D. ran the genetic testing and analysis.

R.A. wrote the case report, did the figure and table.

All authors reviewed the case report and made some enhancements.

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## Figures

Fig. 1. Clinical Timeline



Figure 1

Clinical timeline summarizing the diagnostic work-up and management of a 39-year-old woman with resistance to thyroid hormone beta (RTH $\beta$ ). The timeline outlines initial presentation with elevated FT4/FT3 and non-suppressed TSH, the paradoxical rise in TSH during thiamazole therapy, normal pituitary MRI, subsequent suspicion of hormone resistance, and genetic confirmation of a pathogenic *THRB* variant (p.Arg429Gln). It further illustrates cessation of antithyroid treatment, a short levothyroxine trial, stabilization on beta-blocker therapy, and initiation of family genetic counselling.