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**Case Report**

# Thyroid Hormone Resistance (Positive THRB Gene), Child Case Study

Rawan Aqeel Alharbi[1], Yara Khaled Arfaj[1], Eman Mohammed Alshehri[1*], Mohammed Abdullah Alkhaldi[1]

[1]Prince Sultan Military Medical City, Riyadh, Saudi Arabia

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***Corresponding Author:** Eman Mohammed Alshehri
Prince Sultan Military Medical City, Riyadh, Saudi Arabia

## Abstract

***Introduction*:** Thyroid hormone resistance (RTHβ) is a rare disorder characterized by reduced tissue responsiveness to thyroid hormones (THs). It is primarily caused by mutations in the thyroid hormone receptor beta (THRB) gene. This case describes a two-year-old boy diagnosed with RTHβ following the incidental detection of elevated thyroid hormones during a routine checkup. The clinical presentation, laboratory findings, genetic analysis, and implications for management are discussed, highlighting the complexities of this rare condition. ***Patient concern and Clinical Finding*:** A two-year-old boy was referred to the Pediatric Endocrinology Department due to elevated FT4 and FT3 levels with normal TSH identified in routine blood tests. Born at 36 weeks after an uneventful pregnancy to non-consanguineous parents, the child had normal growth and development until subtle symptoms, such as reduced physical activity, weight loss despite adequate nutrition, and warm, sweaty skin, were observed. Physical examination showed no goiter or ophthalmopathy, with neurological development appropriate for age and weight and height within normal percentiles. Laboratory tests revealed elevated thyroid hormone levels, negative thyroid antibodies, and normal thyroid ultrasound findings. ***Diagnosis/Intervention/Outcomes*:** The diagnosis of resistance to thyroid hormone beta (RTHβ) was confirmed through whole exome sequencing, which identified a heterozygous missense mutation in the THRB gene (c.1313G>A; p.R438H). This de novo mutation ruled out inheritance and suggested a sporadic origin. Regular monitoring of thyroid function tests and clinical follow-ups ensured biochemical stability and vigilance for potential symptoms of thyroid dysfunction. The child remained clinically euthyroid with normal growth and development, showing peripheral adaptation to altered thyroid hormone signaling. Long-term surveillance was recommended to monitor for any late-onset complications or thyroid-related symptoms, with an overall favorable prognosis. ***Conclusion*:** This case illustrates the complexities of diagnosing and managing RTHβ in a pediatric patient. The identification of a THRB mutation provided a definitive diagnosis and emphasized the utility of genetic testing. Long-term follow-up is essential to monitor the clinical course and adjust management as needed. Further studies are required to elucidate the genotype-phenotype correlations in RTHβ and optimize treatment strategies.

**Keywords:** Case report, THRB gene, FT4, Thyroid Hormone Resistance, (FT4) and (FT3).

**Abbreviations:** Thyroid Hormone Resistance (RTH), Thyroid Hormone Receptor beta (THRB), Thyroxine (FT4) and Triiodothyronine (FT3).



## 1. INTRODUCTION

Thyroid hormone resistance (RTH) is a rare autosomal dominant disorder characterized by reduced responsiveness of target tissues to thyroid hormones, despite elevated levels of circulating thyroxine (T4) and triiodothyronine (T3) (Ortiga-Carvalho *et al*., 2014). This condition, often linked to mutations in the thyroid hormone receptor beta (THRB) gene, poses diagnostic and therapeutic challenges due to its diverse clinical presentations and varying biochemical profiles. Recent advancements in molecular genetics have significantly enhanced our understanding of RTH, particularly in pediatric populations.

Despite variable clinical presentations, the defining clinical feature of RTH (Resistance to Thyroid Hormone) is the presence of a goiter without the typical symptoms or metabolic effects associated with thyroid hormone excess. Clinically, patients with RTH can be classified into three categories: generalized resistance (GRTH), pituitary resistance (PRTH), or a combination of both. Mutations in the thyroid hormone receptor (TR) β gene are the underlying cause of RTH, with 122 distinct mutations identified across 300 families. Except for one family with a complete deletion of the TRβ gene, all cases involve minor alterations at the DNA level (Olateju & Vanderpump, 2006).

Refetoff *et al*., in 1967, first described thyroid hormone resistance in a family with elevated T3 and T4 levels and inappropriate thyrotropin (TSH) secretion. This seminal study laid the groundwork for subsequent research by elucidating the clinical and biochemical hallmarks of the condition (Refetoff *et al*., 1967). Also, study done by Takeda *et al*., in 1992, identified mutations in the THRB gene as the primary cause of RTH, providing a molecular basis for the disorder. Their work demonstrated that these mutations impair thyroid hormone receptor function, leading to variable phenotypes ranging from asymptomatic to profound clinical manifestations (Takeda *et al*., 1992). In reviewed over 200 cases of RTH, emphasizing the heterogeneity of clinical presentations, including goiter, attention deficit hyperactivity disorder (ADHD), and growth retardation in children. The authors highlighted the importance of genetic testing in confirming the diagnosis (Weiss & Refetoff, 2000).

Bochukova *et al*., explored genotype-phenotype correlations in RTH, revealing that specific THRB mutations are associated with distinct clinical features. This study underscored the need for personalized approaches to management based on genetic profiles (Bochukova *et al*., 2012). The physiological mechanisms of thyroid hormone action and resistance, focusing on the molecular disruptions caused by THRB mutations. They proposed a framework for understanding the systemic effects of thyroid hormone resistance, including its impact on metabolism and development (Mullur *et al*., 2014). Campi *et al*., in 2015, investigated pediatric cases of RTH, reporting that children often present with hyperactivity and learning difficulties. Their findings emphasized the role of early diagnosis and multidisciplinary management in improving long-term outcomes (Campi *et al*., 2015). Also, Dumitrescu and Refetoff in 2020, provided a comprehensive review of RTH, focusing on advances in molecular genetics and therapeutic strategies. They discussed the use of selective thyroid hormone analogs as a potential treatment option for patients with severe phenotypes (Dumitrescu & Refetoff, 2020). Related to analyzed neurodevelopmental outcomes in children with RTH, finding that early intervention, including cognitive therapies and tailored thyroid hormone replacement, significantly improved developmental trajectories (Ferrara *et al*., 2021). Study done by Luo *et al*., in 2023 reported a case series of pediatric RTH patients with THRB mutations, illustrating the clinical variability and emphasizing the importance of family screening in identifying asymptomatic carriers. Their work reinforced the genetic basis and hereditary nature of the disorder (Luo *et al*., 2023).

The identification of THRB mutations has transformed the diagnostic landscape, enabling precise characterization of the disorder. However, challenges remain in tailoring management strategies to the individual needs of patients. This case report contributes to the growing body of literature by presenting a child with a confirmed THRB mutation, and exploring the clinical, biochemical, and genetic aspects of the condition.

## 2. CASE PRESENTATION

### 2.1 Clinical History

A two-year-old boy was referred to the Pediatric Endocrinology Department following routine blood tests that showed elevated FT4 and FT3 levels with normal TSH. He was born at 36 weeks of gestation, the second child of non-consanguineous parents, after an uneventful pregnancy. The mother had well-controlled gestational diabetes.

The child's growth and development were age-appropriate, and his health was largely unremarkable until the age of two. At that time, the parents observed subtle changes, including reduced physical activity, unexplained weight loss despite adequate nutrition, and warm, sweaty skin.

### 2.2 Physical Examination

**Weight:** At the 50th percentile for age
**Height:** At the 55th percentile for age
**Neurological Development:** Appropriate for age
**Other Findings:** No goiter or ophthalmopathy; skin warm to the touch.

### 2.3 Laboratory Findings and Results

The initial thyroid function tests revealed:
**Elevated FT4:** Measured at 54.5 pmol/L, along with elevated FT3 levels.
**Non-suppressed TSH:** Recorded at 5.79 mIU/L, indicating an unusual pattern for thyroid dysfunction.
**Negative thyroid antibodies:** Tests for anti-thyroid peroxidase, anti-thyroglobulin, and TSH receptor antibodies all returned negative results, ruling out common autoimmune thyroid conditions.
**Normal thyroid ultrasound:** Imaging showed no abnormalities in the thyroid gland's structure.
Over the years, serial thyroid function tests consistently demonstrated persistently elevated FT4 levels accompanied by fluctuating TSH levels. The detailed progression of these results is summarized in the Figure below:

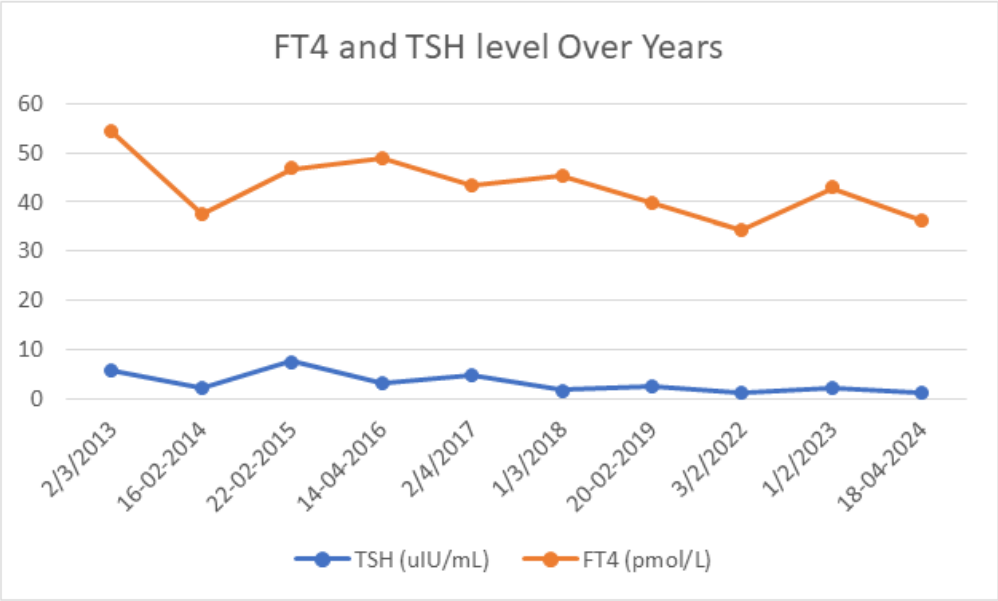


**Figure 1: FT4 and TSH level from Year 2013to 2024**

### 2.4 Genetic Analysis

Whole exome sequencing revealed a heterozygous missense mutation in the THRB gene (c.1313G>A; p.R438H), which is a well-documented pathogenic variant associated with resistance to thyroid hormone beta (RTHβ). This specific mutation leads to an arginine-to-histidine substitution at position 438 in the thyroid hormone receptor beta, impairing its ability to bind thyroid hormone effectively. Such molecular disruption contributes to the hallmark biochemical and clinical features of RTHβ, including elevated levels of thyroid hormones (T3 and T4) with non-suppressed thyroid-stimulating hormone (TSH). Genetic testing of both parents for the same mutation returned negative results, suggesting that this case is a sporadic de novo mutation rather than one inherited from either parent. Sporadic mutations in the THRB gene are relatively uncommon but have been reported in the literature, emphasizing the genetic heterogeneity of RTHβ. Such findings highlight the necessity of comprehensive genetic analyses, especially in cases with no family history of thyroid-related disorders. A sporadic mutation has significant implications for clinical management and genetic counseling. It excludes the likelihood of vertical transmission in immediate family members. Still, it underscores the importance of monitoring for similar presentations in future siblings or descendants due to the possibility of germline mosaicism. Furthermore, this case illustrates the value of advanced diagnostic tools like whole exome sequencing in unraveling rare genetic etiologies of endocrine disorders.

### 3. Follow-Up and Clinical Course:

Throughout the follow-up period, the patient maintained a clinically euthyroid state, demonstrating no signs of overt hyperthyroidism or hypothyroidism. Despite the underlying mutation in the THRB gene, the child exhibited normal growth and developmental milestones, which is a reassuring outcome in cases of resistance to thyroid hormone beta (RTH\u03b2).

Regular monitoring of thyroid function tests, including serum levels of T3, T4, and TSH, was carried out to assess biochemical stability and detect any early deviations that might indicate evolving thyroid dysfunction. Additionally, close clinical observation ensured that symptoms such as weight changes, fatigue, tachycardia, or behavioral alterations\u2014commonly associated with thyroid imbalances\u2014did not develop over time.

The normal growth and development trajectory suggest that the patient's peripheral tissues may have adapted to the altered thyroid hormone signaling caused by the THRB mutation. This adaptation highlights the heterogeneity of RTH\u03b2 presentations, as some individuals remain asymptomatic or minimally affected despite biochemical abnormalities.

These findings underscore the importance of personalized management plans for patients with RTH\u03b2, which include routine follow-ups, tailored thyroid function tests, and vigilance for subtle clinical changes. The absence of overt thyroid-related symptoms in this patient provides an optimistic prognosis, but it emphasizes the necessity of continued long-term surveillance to address potential complications, including learning difficulties, cardiovascular effects, or metabolic imbalances that might emerge later in life.

## 4. DISCUSSION

### 4.1 Pathophysiology

Resistance to thyroid hormone beta (RTHβ) is a rare genetic disorder caused by mutations in the THRB gene, which encodes the thyroid hormone receptor beta

(TRβ). This receptor plays a critical role in mediating thyroid hormone actions across various tissues, including the hypothalamus, pituitary gland, liver, and heart. Mutations in the THRB gene reduce the receptor's affinity for thyroid hormones, impairing normal signaling and leading to tissue-specific physiological responses.

The phenotypic variability observed in RTHβ is largely attributed to differential tissue sensitivity to thyroid hormones. Some tissues may exhibit hypothyroid-like features, such as growth retardation and cognitive delays, due to impaired receptor function, while others may display hyperthyroid-like symptoms, such as tachycardia and increased sweating, caused by excessive thyroid hormone activity. This variability underscores the complex interplay between receptor functionality and hormone action across different tissues, as highlighted in studies by Refetoff *et al*., (1993) and Beck-Peccoz *et al*., (2004).

### 4.2 Diagnostic Challenges

Diagnosing RTHβ can be challenging due to its biochemical and clinical overlap with other thyroid disorders. The classic biochemical hallmark of RTHβ includes elevated levels of free thyroxine (FT4) and triiodothyronine (FT3) with normal or elevated thyroid-stimulating hormone (TSH) levels. However, this pattern is not exclusive to RTHβ and necessitates differentiation from conditions such as TSH-secreting pituitary adenomas, familial dysalbuminemic hyperthyroxinemia, and laboratory assay interference (McDermott *et al*., 2002).

Genetic testing remains the gold standard for confirming the diagnosis, as it identifies pathogenic mutations in the THRB gene. In this case, whole exome sequencing confirmed the presence of a heterozygous missense mutation (c.1313G>A; p.R438H) in the THRB gene, a mutation widely reported in cases of RTHβ (Weiss & Refetoff, 2000). Importantly, genetic testing also excluded familial inheritance, confirming this case as a sporadic de novo mutation.

### 4.3 Management

The management of RTHβ is individualized, focusing on the severity of symptoms and biochemical findings. For asymptomatic or mildly affected patients, a conservative approach involving regular follow-ups and thyroid function monitoring is often sufficient. Studies have shown that in many such cases, patients remain clinically stable without requiring pharmacological intervention (Beck-Peccoz *et al*., 2004).

In cases where patients experience significant symptoms, such as tachycardia, palpitations, or behavioral disturbances, beta-blockers can be used to mitigate these hyperthyroid-like effects. For example, Martino *et al*., (2009) documented the successful use of beta-blockers in managing cardiac symptoms associated with RTHβ. However, treatment must be carefully tailored to avoid exacerbating hypothyroid-like symptoms in other tissues.

In this case, the absence of overt clinical symptoms and normal growth and development allowed for a conservative management strategy. Regular monitoring of thyroid function tests and clinical evaluations ensured early detection of any changes, enabling timely intervention if needed. This approach aligns with recommendations from McDermott *et al*., (2002), which emphasize vigilance in asymptomatic patients to maintain a euthyroid state and prevent long-term complications.

## 5. CONCLUSION

This case underscores the importance of a multidisciplinary approach in managing resistance to thyroid hormone beta (RTHβ). Effective management requires the integration of genetic insights, biochemical evaluations, and clinical observations to address the unique challenges posed by the condition. The variability in tissue responses to thyroid hormones highlights the need for an individualized care plan tailored to each patient’s specific clinical presentation to ensure optimal outcomes.

The identification of a THRB mutation in this case provided a definitive diagnosis, reinforcing the critical role of genetic testing in diagnosing RTHβ. This approach not only confirmed the diagnosis but also excluded alternative conditions with similar biochemical profiles. The case also illustrates the complexities of diagnosing and managing RTHβ in pediatric patients, emphasizing the need for thorough long-term follow-up to monitor the clinical course, ensure biochemical stability, and make timely adjustments to management strategies as needed.

Furthermore, this case highlights the necessity for ongoing research to deepen our understanding of the pathophysiology of RTHβ. Studies exploring genotype-phenotype correlations are particularly essential to unravel the mechanisms underlying the variable clinical presentations observed in RTHβ patients. Such research is crucial for optimizing diagnostic accuracy and refining treatment strategies, thereby improving outcomes for affected individuals.

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