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Case Report

Concurrent *THRB* and *DUOX2* variants in a patient detected via newborn screening for congenital hypothyroidism: a case of resistance to thyroid hormone

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Highlights

- We report a molecularly confirmed case of RTH complicated by *DUOX2* defect.
- Our patient exhibited normal development without treatment.
- Comprehensive genetic analysis is valuable in patients with RTH with an atypical presentation.

Abstract. Most patients with resistance to thyroid hormone (RTH) test negative in newborn screening (NBS) for congenital hypothyroidism (CH). Here, we present a case of RTH diagnosed through NBS. The patient presented to us after her NBS for CH revealed high TSH (23.4 μIU/mL) and free T4 (FT4) (5.40 ng/dL) levels. Apart from tachycardia, she exhibited no other manifestations related to excess or deficiency of thyroid hormones. A confirmatory test replicated the findings, showing elevated serum TSH levels (35.7 μIU/mL) along with high FT4 levels (5.84 ng/dL). Ultrasonography showed marked thyroid gland enlargement (> +4 SD). Targeted next-generation sequencing of genes associated with genetic thyroid disorders revealed a previously reported *THRB* variant, p.Gly345Cys. Unexpectedly, two biallelic *DUOX2* variants (p.His678Arg and p.Arg1334Trp) were also detected. At her last visit, no significant issues were observed with neurological development, growth, bone maturation, or gastrointestinal symptoms related to thyroid function at the age of 1 year, without treatment for RTH and CH. During follow-up, the TSH and FT4 levels gradually decreased. In conclusion, we report a patient with simultaneous RTH and *DUOX2* defects, demonstrating the value of conducting a comprehensive analysis of multiple genes associated with thyroid diseases to better comprehend the pathogenesis in patients with atypical thyroid-related phenotypes.

Key words: thyroid hormone resistance syndrome, *THRB*, *DUOX2*, newborn screening

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Introduction

Resistance to thyroid hormone (RTH), initially described in 1967, is a rare genetic disorder characterized by reduced responsiveness of target organs to thyroid hormones (1). Clinically, patients with RTH exhibit elevated thyroid hormone levels alongside non-suppressed TSH, a condition referred to as the syndrome of inappropriate TSH secretion (2). Approximately 85% of RTH cases result from genetic defects in *THRB* (3), which encodes thyroid hormone receptor (TR) β, and typically follows an autosomal dominant trait (4). Although precise incidence data for RTH are lacking, it is estimated to affect one in 20,000-40,000 live births (5–8).

Two TR subtypes exist, TRα and TRβ, and their expression patterns differ for each organ. Because RTH pathogenesis can be attributed to abnormal TRβ function, the organs with predominant TRβ expression, such as the hypothalamus, pituitary gland, and liver, exhibit a reduced response to thyroid hormones. This results in increased TSH secretion from the pituitary gland and compensatory elevation of T3 and T4 levels. The heart, gastrointestinal tract, and central nervous system, characterized by predominant TRα expression, are susceptible to increased thyroid hormone levels (9). Patients may be asymptomatic or present with goiter, sinus tachycardia, learning disabilities with or without hyperactive behavior, or developmental delays (5). This wide array of clinical manifestations may stem from the severity of hormone resistance, effectiveness of compensatory mechanisms, and genetic factors other than *THRB* (3,10). In the diagnosis of RTH, proactive suspicion based on clinical symptoms and laboratory results, accurate thyroid hormone measurements to exclude false increases, and genetic analyses are important. Herein, we report the case of a girl with RTH who presented with an atypical clinical presentation, and whose molecular diagnosis was confirmed through comprehensive genetic analysis.

Case Report

The proband, a girl, was the first child of healthy, unrelated parents who had migrated from China to Japan. The mother was diagnosed with gestational diabetes mellitus in the third trimester of pregnancy. The proband was born via spontaneous vaginal delivery at 39 wk and 2 d of gestation. Her birth weight was 3,000 g (0.0 SD), and birth length was 49.5 cm (+0.5 SD). No history of thyroid disease was noted in second-degree relatives. Because of the high levels of TSH and free T4 (FT4) observed in the newborn screening (NBS) conducted at ages 4 and 12 d (blood-spot TSH 23.4 μIU/mL and 38.4 μIU/mL; cut-off = 9.0, FT4 5.40 ng/dL and 5.27 ng/dL; cut-off = 4.0, respectively), she was referred to us at the age of 21 d. She had normal weight gain (+37 g/d). She exhibited no manifestations related to hyperthyroidism or hypothyroidism, except for mild tachycardia (182 bpm, reference: 143, 133–154; median, 25th–75th percentile, respectively (11)). Blood tests confirmed the abnormal thyroid profile, revealing elevated serum levels of TSH (35.7 μIU/mL, reference: 0.72–12.7), FT4 (5.84 ng/dL, reference: 0.89–2.2), and free T3 (FT3) (18.8 pg/mL, reference: 1.95–6.2), as measured by Elecsys® TSH, FT4, and FT3 assays (Roche Diagnosis). Additionally, the serum Tg level was markedly elevated (436 ng/mL, reference: 8.8–129). Anti-TSH receptor, anti-thyroglobulin, and thyroid peroxidase antibodies were negative. The size of the distal femoral epiphyses appeared normal. Ultrasonography revealed a diffuse goiter (width multiplied by the thickness of the area, right lobe +4.5 SD, left lobe +4.8 SD) (12) and enhanced blood flow (**Fig. 1B**). Magnetic resonance imaging revealed a normal pituitary gland. At 1 mo of age, a thyrotropin-releasing hormone stimulation test was performed, revealing high baseline and stimulated TSH levels (23.8 μIU/mL and 113.9 μIU/mL, respectively). To exclude the possibility of immunologically falsely high values of thyroid hormones, we measured thyroid hormones using the LC-MS/MS method (13). As expected, the levels of total T3 (2.22 ng/mL; reference: 0.8–2.0), total T4 (164 ng/mL; reference: 47–115), and reverse T3 (0.77 ng/mL; reference: 0.06–0.26) were all higher than the reference intervals. Given the clinical diagnosis of RTH, we opted not to initiate immediate treatment but to closely monitor her for any symptoms indicative of thyroid hormone excess or deficit. We observed gradual decreases in TSH, FT4, FT3, and Tg levels. At age of 9 mo, the levels were as follows: 8.62 μIU/mL (reference: 0.73–8.92), 2.91 ng/dL (reference: 0.92–1.99), 6.9 pg/mL (reference: 2.15–5.92), 248.5 ng/mL (reference: 8.8–129) respectively. Her heart rate was above the upper normal limit in early infancy, gradually normalized in late infancy (**Fig. 1A**). She was formula fed during infancy and showed normal growth at her last visit at the age of 1 year (**Fig. 1C**). Early developmental milestones were achieved at appropriate ages: holding her head up at 3 mo of age, rolling from prone to supine at 4 mo of age, sitting up without support at 6 mo of age, and standing alone at 10 mo of age. No significant difference was observed between her chronological age and bone age at 9 mo of age.

We investigated the thyroid function of her parents and found that her father had similar test results, with elevated FT4 levels without suppression of TSH (TSH 1.76 μIU/mL, FT4 2.5 ng/dL) (**Fig. 2A**). His weight was 66.0 kg, and he was 176.1 cm tall (body mass index 21.3 kg/m^2). His blood pressure was 104/78 mmHg, and his pulse rate was 99 bpm, regular (reference: 71, 61–76; median, 25th–75th percentile, respectively (14)). Electrocardiography revealed sinus tachycardia. Thyroid ultrasound showed no thyroid gland enlargement (right lobe: 48.8 × 19.7 × 18.5 mm; left lobe: 44.9 × 23.2 × 19.5 mm) and detected a left-sided cystic nodule measuring 5.7 × 4.9 × 2.5 mm.

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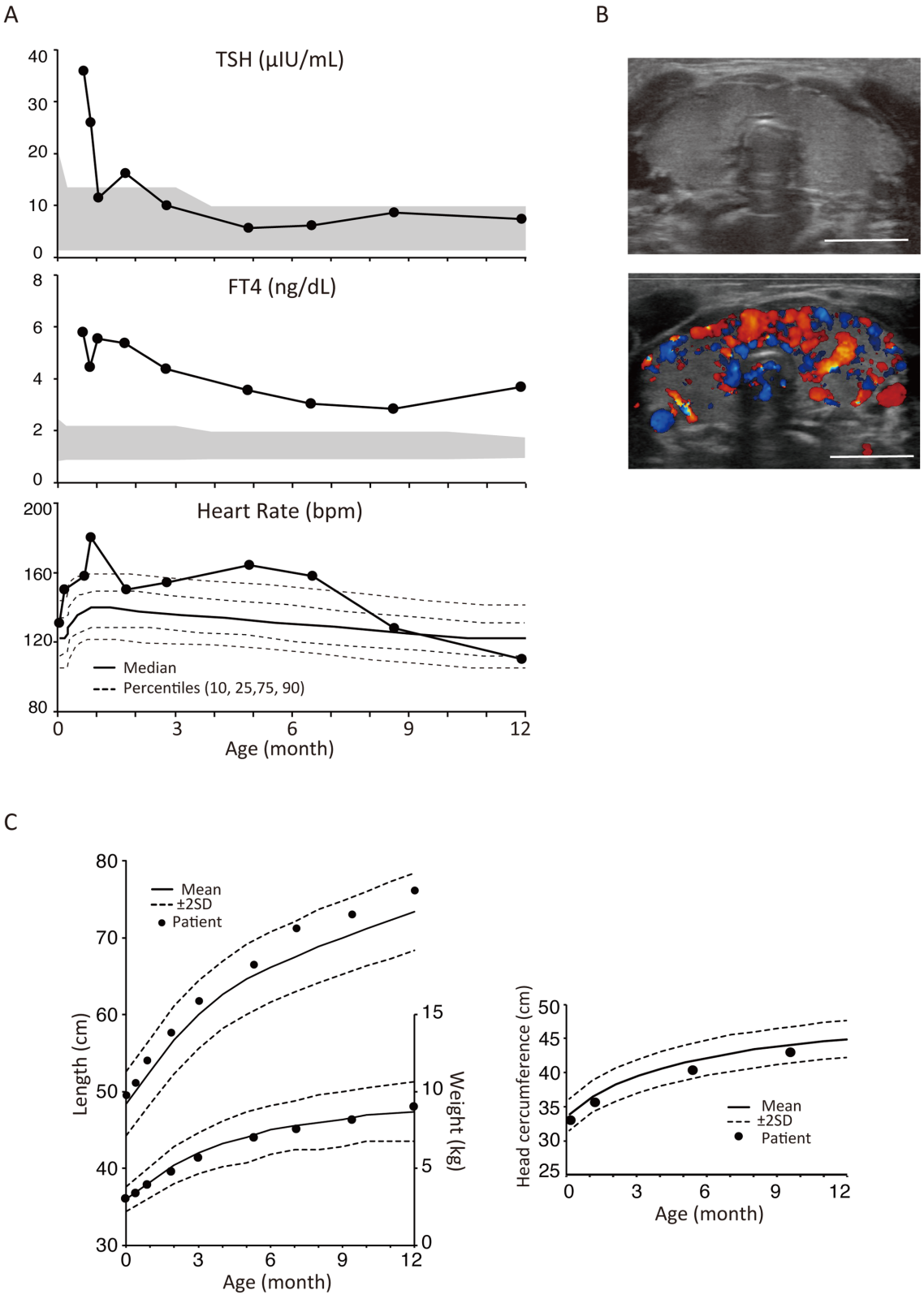

Fig. 1. Clinical findings of the patient. **A:** Serum TSH, free T4 (FT4), and heart rate gradually decreased over time. Upper and middle panel: TSH and FT4 were measured by immunoassay (ECLIA, Elecsys®, Roche Diagnostics). The gray shaded area indicates a range of 2.5th–97.5th percentile range of TSH and FT4 according to age (33). Lower panel: Dashed lines denote the percentile ranges (10, 25, 75, 90th) of heart rate according to age (11). **B:** Ultrasonography of the thyroid gland in the patient at age 1 mo. The thyroid gland was markedly enlarged and showed increased blood flow. The widths and thicknesses of the thyroid glands were calculated as follows: 12.6 mm and 11.2 mm (right lobe), 13.3 mm and 12.0 mm (left lobe), respectively. Scale bar indicates 10 mm. **C:** Growth charts of the patient displaying normal growth. Left panel: length and weight. Right panel: head circumference. Data are plotted on a standard growth chart of Japanese girls (34). Solid and dotted lines represent the mean and ± 2 SD.

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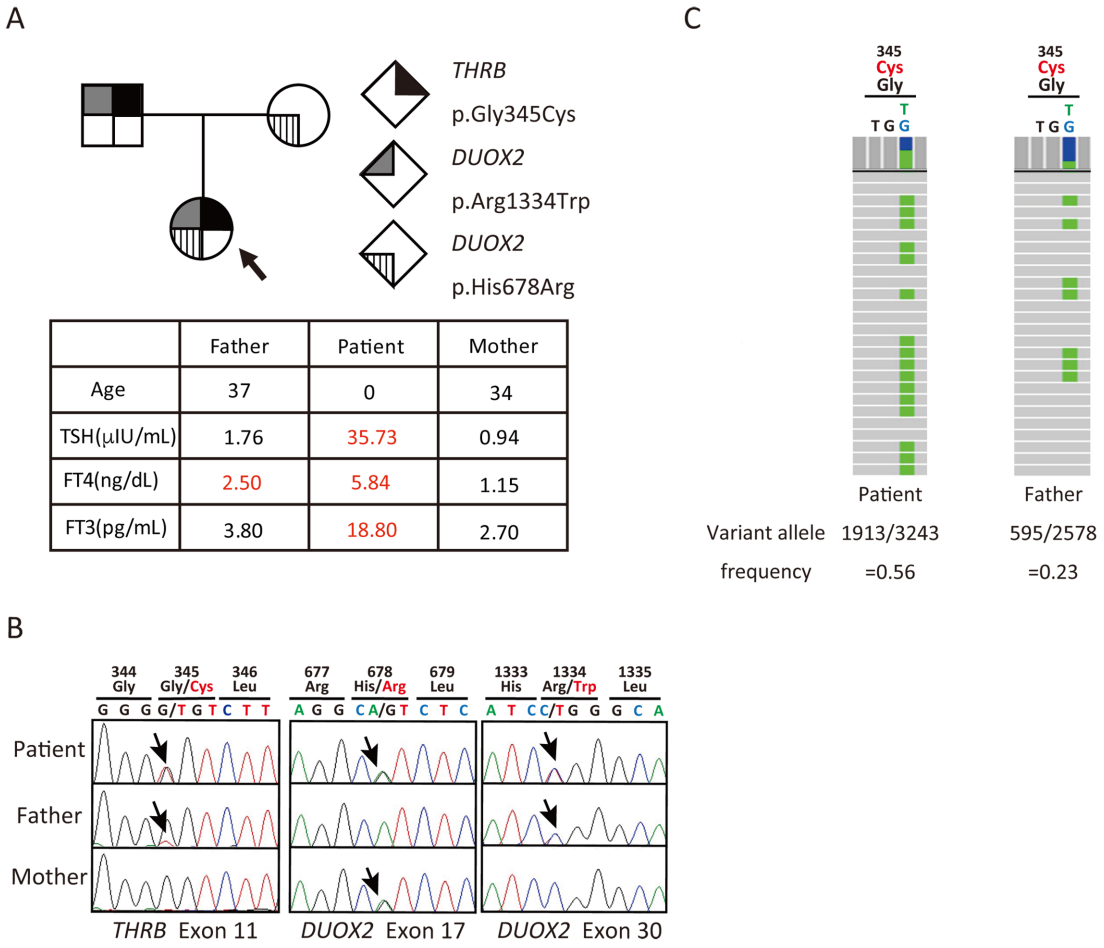

	Father	Patient	Mother
Age	37	0	34
TSH(μIU/mL)	1.76	35.73	0.94
FT4(ng/dL)	2.50	5.84	1.15
FT3(pg/mL)	3.80	18.80	2.70

Fig. 2. Family genetic data. **A:** Pedigree and family thyroid function test results. Values in red signify values higher than the upper limit of normal. Elevated thyroid hormone levels without TSH suppression were observed in both the patient and her father. **B:** Partial sequence chromatograms of *THRB* and *DUOX2* showing variants in the patient and her parents (arrows). The signal from the *THRB* variant allele was less intense than that from the wild-type allele in the chromatogram of the father, suggesting somatic mosaicism of *TRHB* p.Gly345Cys. **C:** The results of the sequenced variant allele frequency analysis were visualized using Integrative Genomics Viewer. Somatic mosaicism was confirmed in the father of the patient.

Genetic Study

Written informed consent for genetic studies was obtained from the parents of the proband. Genomic DNA was extracted from peripheral blood leukocytes of the proband and her parents. For the proband, a next-generation sequencing library was prepared using a QIAseq targeted DNA custom panel (QIAGEN, Hilden, Germany) designed to target 18 known thyroid-related genes (*DUOX2, DUOXA2, FOXE1, IGSF1, IYD, NKX2-1, PAX8, SLC26A4, SLC5A5, TBL1X, TG, IRS4, THRB, TPO, TRH, TRHR, TSHB,* and *TSHR*). Sequencing was performed using a next-generation sequencer MiSeq (Illumina Inc., San Diego, CA, USA). We identified a previously reported disease-causing *THRB* variant (c.1033G>T, p.Gly345Cys) in the heterozygous state, leading to the molecular diagnosis of RTH (15). Additionally, we detected two heterozygous loss-of-function *DUOX2* variants: one was a previously reported disease-causing missense variant p.Arg1334Trp (16), and the other was a functional single nucleotide polymorphism p.His678Arg (17). Family analysis using PCR-based Sanger sequencing unveiled that the *THRB* variant was inherited from her father, and the two *DUOX2* variants were transmitted from each parent (**Fig. 2A**). Interestingly, during the paternal analysis of the *THRB* variant, we observed a lower intensity of the signal derived from the variant allele than from the wild-type allele, suggesting a somatic mosaic state (**Fig. 2B**). For a more rigorous estimation of the somatic mosaic state of the father, we evaluated the variant allele frequency. The genomic region encompassing the *THRB* variant was PCR-amplified from leukocytic genomic DNA of both the patient and her father. Next-generation sequencing libraries were prepared using the NEBNext Ultra II FS DNA Library Prep Kit for Illumina (New England Biolabs, Ipswich, MA, USA) and then sequenced using a MiSeq sequencer. We visualized the reads using the Integrative Genomics Viewer (18) and calculated the variant allele frequency by dividing the variant

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read counts by the total read counts at the nucleotide of interest, *THRB* c.1033. The estimated variant allele frequencies in the patient and her father were 0.56 and 0.23, respectively (**Fig. 2C**).

Discussion

We present a case of RTH with *DUOX2* defect, the most common cause of congenital hypothyroidism (CH) diagnosed within NBS. The patient exhibited normal growth and neurological development for up to 1 yr without treatment. To date, eight patients with RTH have been diagnosed within the framework of NBS (**Table 1**) (6, 7, 19, 20). Generally, patients with RTH have normal or mildly elevated TSH levels (7) that may not be detected by TSH-based NBS. Accordingly, six of the previously reported patients were diagnosed with NBS based on simultaneous TSH and FT4 measurements (**Table 1**). The remaining two patients had elevated blood spot TSH levels detected by TSH-based NBS (**Table 1**) (19, 20). TSH levels in patients with *THRB* frameshifts and truncations are reported to be higher than the TSH values in patients with *THRB* single amino acid deletions or single amino acid substitutions (21). Our patient, with a *THRB* single amino acid substitution, showed comparable TSH elevation to patients with *THRB* frameshifts and truncations, suggesting additional factors.

Although most patients with RTH are clinically euthyroid and necessitate only watchful waiting (3, 22), those with overt CH require prompt levothyroxine supplementation to prevent developmental delays. Rarely, RTH can be complicated by CH, as documented in six reports: five cases attributed to ectopic thyroid (23–27) and one case due to *SLC5A5* defects (28). In contrast to our patient, all other reported cases initially presented with typical CH symptoms and were suspected of RTH complications because they required a supraphysiological dose of levothyroxine to normalize serum TSH levels. We refrained from prescribing treatment for our patient, neither for RTH nor CH, due to the limited symptoms (goiter and mild tachycardia) alongside compensatory thyroid hormone elevation. Dual oxidase (DUOX) 2, encoded by *DUOX2*, plays a crucial role in thyroid hormone synthesis by producing H_2O_2. Biallelic *DUOX2* loss-of-function variants are known to cause CH (29). Specifically, the p.Arg1334Trp-DUOX2 protein showed only 24% of normal H_2O_2 production (30), whereas the p.His678Arg-DUOX2 protein demonstrated 80% of normal H_2O_2 production (29). The relatively high residual activity of p.His678Arg-DUOX2 protein may account for the synthesis of thyroid hormones in our patient in response to TSH stimulation.

The father of the patient carried a *THRB* variant in a somatic mosaic state. To date, only two patients with somatic mosaic *THRB* variants have been described (31, 32). One patient, diagnosed with RTH through a family study (p.Arg338Trp), remained asymptomatic despite having high FT4 levels without suppression of TSH levels. The mosaicism ratio of the variant in peripheral blood was 8.6% (32). Another patient, with the p.Ala317Thr variant, exhibited signs of RTH such as goiter, tachycardia, and diarrhea, with 12% mosaicism in peripheral blood (31). The father of our patient exhibited 23% mosaicism for p.Gly345Cys in peripheral blood and was diagnosed with symptomatic RTH based on mild tachycardia. However, the presence or absence of symptoms cannot be solely explained by the mosaicism rate in peripheral blood. Further research is necessary to gain a better understanding of the clinical characteristics of patients with *THRB* mosaicism.

In conclusion, we present a case of RTH accompanied by a *DUOX2* defect. Our findings highlight the significance of conducting comprehensive genetic

Table 1. Summary of findings in patients diagnosed with RTH within the context of NBS

Patient	NBS method	Blood-spot TSH (μIU/mL)	Blood-spot FT4 (ng/dL)	Serum TSH (μIU/mL)	Serum FT4 (ng/dL)	Serum FT3 (pg/mL)	Serum tT3 (ng/mL)	Genotype	Treatment	Reference
1	TSH + FT4	1.4	4.45	3.21	3.68	8.03	NA	p.Thr277Ile	NA	(6)
2	TSH + FT4	1.7	5.72	11.34	4.77	13.95	NA	p.Thr448Hisfs*17 (described as c.1627_1628insC in ref 6)	NA	(6)
3	TSH + FT4	NA	NA	1.99	3.1	NA	3.0	p.His435Arg	NA	(7)
4	TSH + FT4	NA	NA	6.60	2.6	NA	3.4	p.His436Arg	NA	(7)
5	TSH + FT4	NA	NA	2.39	2.8	NA	3.2	p.His437Arg	NA	(7)
6	TSH + FT4	NA	NA	4.64	2.8	NA	NA	p.His438Arg	NA	(7)
7	TSH	13.1	NA	4.30	3.7	6.70	NA	p.Pro453Thr	NA	(19)
8	TSH	198	NA	34.0	> 8.0	> 25.0	NA	p.Glu449Aspfs*11	liothyronine therapy	(20)
9	TSH + FT4	23.4	5.40	35.73	5.84	18.80	2.22	p.Gly345Cys	No	Present case

RTH, resistance to thyroid hormone; NBS, newborn screening; NA, not available; FT4, free T4; FT3, free T3; tT3, total T3.

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analysis in patients with RTH, particularly those presenting with atypical clinical features.

Conflict of interests: The authors have no conflicts of interest to declare.

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