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Clinical Characteristics and Genotype-phenotype Correlation in Turkish Patients with a Diagnosis of Resistance to Thyroid Hormone Beta

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What is already known on this topic?

Variants in the *THRB* gene are the most common cause of resistance to thyroid hormone (RTH), termed RTH beta (RTHβ). RTHβ is a rare condition, and is mostly asymptomatic. Therefore, lack of awareness may lead to misdiagnosis, unnecessary tests or inappropriate management of the patient.

What this study adds?

In the present study, evaluating the clinical and genetic characteristics of a series of 30 Turkish patients with genetically confirmed RTHβ in comparison to variant-negative patients, the *THRB* gene variant database was expanded with three novel variants. Furthermore, the results provide evidence for prioritizing individuals for genetic analysis by comparing RTHβ patients with and without a detected variant in THRB.

Abstract

Objective: Resistance to thyroid hormone beta (RTHβ) is a rare disorder characterized by a fairly heterogeneous clinical presentation due to varying degrees of tissue response to thyroid hormone. The present study aimed to evaluate the clinical and laboratory features and genotype-phenotype relationship of Turkish patients with RTHβ.

Methods: Patients who underwent a *THRβ* gene analysis between September 2019 and September 2023 were retrospectively reviewed.

Results: Fifty patients with the clinical features of RTHβ syndrome or a family history of an index case were included. A total of eight different heterozygous pathogenic/likely pathogenic missense variants, three of which were novel, were detected in *THRB* in 30 patients from 8 unrelated families. Although most patients with RTHβ were asymptomatic, seven patients exhibited various symptoms. Moreover, seven patients had received various treatments before diagnosis. Thyroid autoantibody was positive in 23% of all cases with a variant,

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and goitre was detected in 56% of children with a variant. While thyroid nodules were detected in seven adult patients, two adults had been diagnosed with papillary thyroid cancer. One child had attention-deficit disorder, learning disability, and type 1 diabetes mellitus. Of the 20 patients without a variant, TSHoma was detected in one.

Conclusion: The present study provides an overview of clinical and genetic characteristics of patients with genetically confirmed RTHβ and expanded the *THRB* gene variant database with three novel variants. Although most patients with RTHβ are asymptomatic, molecular genetic analysis of the *THRB* gene and regular follow-up because of the apparent risk of concurrent autoimmune diseases or thyroid cancer is warranted.

Keywords: Thyroid hormones, resistance to thyroid hormone, *THRB* gene, autoimmune thyroid disease, goitre

Introduction

Defects in signaling of the thyroid hormones (TH), tetraiodothyronine (T4) and triiodothyronine (T3), TH cell membrane transport, TH metabolism, or TH action lead to reduced TH sensitivity (1,2). TH action defect is characterized by reduced response to circulating TH in target tissues, termed resistance to TH (RTH). Variants in the TH receptor gene are responsible for the etiology of the majority of RTH (3,4). There are two distinct subtypes of the TH receptor (TR); TRα and TRβ. Variants in TH receptor beta (*THRB*) gene are the most common cause of RTH, termed RTHβ (5). The prevalence of RTHβ has been reported to vary from 1 in 40,000 to 1 in 18,750 live births, with no gender predominance (6,7).

RTHβ is characterized by inappropriately normal or elevated thyroid-stimulating hormone (TSH) concentrations concurrent with extremely elevated TH levels (3). RTHβ syndrome is mainly characterized by reduced effects of T3 at the cellular and tissue level (8). Excessive TH secretion usually compensates for the impaired sensitivity in peripheral tissues. Therefore, patients with RTHβ syndrome are typically euthyroid, thereby achieving normal growth and mental development. However, elevated TH may lead to thyrotoxic symptoms, such as tachycardia in heart tissue where TRα serves as a dominant receptor or cause irritability. Although rare, patients may experience clinical features of hypothyroidism, in cases with variants that severely prevent TH receptor activity (1). These variable manifestations are in part due to variable tissue expression of the TR subtypes (9). The severity of the symptoms varies among individuals, even those from the same family with an identical *THRB* gene variant (10).

TRβ is a ligand-dependent transcription factor consisting of two functional domains: the ligand-binding domain at the carboxyl terminal, which recognizes T3, and the DNA-binding domain. The majority of the variants are located in three clusters enriched with CpG dinucleotide hot spots in the carboxy terminus of TRβ and result in mutant proteins (11). Although most cases have heterozygous variants, a few cases have harbored homozygous variants (4,12). Most variants are single nucleotide substitutions leading to an amino acid change or, less frequently, to a truncated protein. Besides, nucleotide insertions, deletions, and duplications have also been described, resulting in frame-shift and nonsense variations (8). While 75% of cases with RTHβ syndrome have a dominant inheritance, it may also occur due to a *de novo* pathogenic variant (1). Of note, the underlying molecular defect can not be detected in about 15% of individuals with the RTHβ phenotype and this condition is referred to as "TR-RTH unspecified" (13).

There are few studies evaluating the molecular genetic analysis of patients with RTHβ syndrome from Türkiye. Firstly, Poyrazoğlu et al. (14) reported a variant in the *THRB* gene in a Turkish family. Following this report, Guran et al. (15) reported the treatment outcome of their patient with the *THRB* gene variant. Işık et al. (16) highlighted the underestimation of RTHβ diagnosis in a family whose index case was misdiagnosed as thyrotoxicosis and treated with antithyroid medication. As RTHβ is rare, and most patients are asymptomatic, lack of awareness may lead to misdiagnosis, unnecessary tests, or inappropriate patient management. The aim of the present study was to evaluate the clinical and laboratory features, and genotype-phenotype relationship of a series of Turkish patients with RTHβ syndrome due to *THRB* gene variants.

Methods

Patients

A retrospective examination was conducted of all patients and their families who underwent *THRB* (NM_001354712.2) gene analysis at Ankara Bilkent City Hospital, Pediatric Endocrinology Clinic, and Endocrinology and Metabolism Clinic with a presumptive diagnosis of RTHβ between September 2019 and September 2023. The study was approved by the Clinical Research Ethics Committee of Ankara Bilkent City Hospital with decision number: 23-5676, date: 22.11.2023. The chief complaints, age of the diagnosis, sex, treatment history, body weight, height, body mass index (BMI), standard deviation scores (SDS),

pulse rate, serum TSH, free T4 (fT4), and free T3 (fT3) concentrations, anti-thyroglobulin antibody (Tg-Ab), and antithyroid peroxidase antibody (TPO-Ab) results of the patients were extracted from the patients' files. Pituitary magnetic resonance imaging (MRI) findings, thyroid ultrasound, echocardiography, and genetic analysis results were evaluated. The thyroid function tests of all patients undergoing molecular genetic analysis were double-checked, as lab and assay-specific variations could potentially affect correct phenotyping and thus pick-up rate for a variant. Besides, none of the patients from our cohort were using biotin or any medication that could interfere with the TH measurement.

All patients were evaluated for goitre. In children, the volume of each lobe was calculated using the formula of length × width × depth × 0.52. The thyroid volume was determined as the sum of both lobes and then SDS were calculated using age- and sex-specific references (17). Values above 2 SDS were considered to be goitre in children. In adults, the thyroid volume of each lobe was calculated using the formula of V (mL) = 0.479 × width (cm) × depth (cm) × length (cm) (18). A thyroid volume above 10 mL in women and 15 mL in men was considered to represent goitre (19). The hormonal profile of patients with a pathogenic or likely pathogenic variant was compared with age and sex-matched healthy controls. The fT4/fT3 ratio was calculated after unifying fT4 and fT3 units as pmol/L.

Molecular Genetic Analyses

Genomic DNA was extracted from peripheral blood leukocytes. For the index patients, all of the coding exons and exon-intron boundaries of the *THRB* gene were amplified by specific primers via polymerase chain reaction (PCR). After cycle sequencing, all PCR products were purified and sequenced on an ABI 3100 Genetic Analyzer (Applied Biosystems®, California, USA). All the sequences were aligned to the reference genome and analyzed using SeqScape® Software (Applied Biosystems®, California, USA). For the relatives of the probands, only variant-associated exonic primers were used and were analyzed with Sanger sequencing. All variants were interpreted according to the American College of Medical Genetics and Genomics Guidelines (20). Written informed consent was obtained from all patients/their legal guardians.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences, version 24.0 (IBM Corporation, Armonk, NY, USA). The mean and standard deviation (SD), median and quartile values of numerical variables were calculated. Categorical variables were expressed as frequency and percentages (%). Shapiro-Wilk test was used to evaluate the normal distribution of data. Normally distributed numerical variables were evaluated using the Student's t-test, and the Mann-Whitney U test was used if the parametric test assumptions were not met. Chi-square analysis and Fisher's exact tests were used to compare categorical variables. A $p < 0.05$ was considered to indicate statistical significance.

Results

The study included 50 patients with the clinical features of RTHβ syndrome or a family history of an index case. All participants underwent *THRB* gene analysis. Thirty patients from eight unrelated families were found to have pathogenic/likely pathogenic variants in the *THRB* gene. Clinical characteristics and hormonal features of patients with a pathogenic variant are shown in Table 1. Variant characteristics and classifications detected in our cohort are displayed in Table 2.

The number of children and adults with a pathogenic or likely pathogenic variant was 16 [female/male (F/M): 11/5] and 14 (F/M: 7/7), respectively. While 12 of these adults were family members of our pediatric patients, two families (family 7 and 8) of two adult patients could not be evaluated because they were either deceased or unwilling to participate in the study. Furthermore, the thyroid function test results and molecular genetic analysis of the parents of children with a likely pathogenic variant from Family 6 were normal, suggesting a *"de novo"* variant. The pedigrees of families 1, 2, 3, 4, 5, and 6 are presented in Figure 1. The median (1st and 3rd quartile) age in children with a pathogenic or likely pathogenic variant was 9.7 (5.2-11.4) years, and the median (1st and 3rd quartile) age in adults with a pathogenic or likely pathogenic variant was 36 (33.8-46) years. All children had a height SDS above -2 SD. BMI-SDS was within the normal range in all children except for two cases with malnutrition (case 3-6 from family 2 and 3-1 from family 5) (Table 1). One of the children (3-1 from family 5) had a diagnosis of type 1 diabetes mellitus (T1DM). While 23 of the 30 patients were asymptomatic, seven (23.3%) had various symptoms [two patients had palpitations, two had goitre, one had sweating, one had anxiety, and one had attention-deficit disorder (ADD), and learning disability (LD)]. Seven (23.3%) had received various forms of treatment at other centres before the diagnosis of RTHβ (Table 1).

Table 1. Clinical and laboratory findings of the patients with *THRB* gene pathogenic or likely pathogenic variants

Family no	Individual	Sex	Age at dx years	Initial presentation	Previous treatment	Tachycardia	Height cm (SDS) BMI (SDS)	FT3 ng/L (adult: 2.3-4.2) (children: 3-4.7)
1	1-1	M	55	Asymptomatic	None	No	NA	NA
	2-1	F	36	Asymptomatic	None	No	153 25.6	4
	2-3	F	35	Palpitation	Triiodothyronine sodium	Yes	157 28.3	4.7
	3-1	F	10.5	Asymptomatic	None	No	142.7 (0.14) 15.9 (-0.71)	7.5
	3-2	F	6.9	Asymptomatic	None	No	115 (-1) 13.6 (-1.3)	8.3
	3-3	F	9.9	Asymptomatic	None	No	127.7 (-1.5) 13.9 (-1.62)	6
	3-4	F	4.9	Asymptomatic	None	No	104.5 (-0.66) 14.8 (-0.43)	7.3
	3-5	M	13.5	Asymptomatic	None	No	153 (-0.97) 15.4 (-1.86)	7.3
2	1-2	F	56	Goitre	NA	No	153 38.4	6.2
	2-1	M	33	Asympotomatic	None	No	178 24.9	7.2
	2-3	M	40	Asympotomatic	None	No	NA	NA
	2-5	M	33	Asympotomatic	None	No	175 24.4	6.9
	3-1	F	11.5	Asymptomatic	Propranolol, mmz	No	152 (0.36) 21.9 (1)	9
	3-2	M	17.1	Asymptomatic	None	No	178 (0.57) 27.1 (1.38)	8.9
	3-3	F	10.1	Sweating	Propranolol	No	144.7 (0.95) 17.1 (0.01)	7.6
	3-4	F	1.5	Asymptomatic	None	No	80 (0.49) 16.1 (-0.08)	9.4
	3-5	M	1.1	Asymptomatic	None	No	75.8 (-0.67) 16.3 (-0.51)	10.9
	3-6	F	7.8	Asymptomatic	None	No	119 (0.89) 16.4 (-2.46)	7.8
3	2-1	M	36	Goitre	None	No	174 27	5.77
	2-3	F	19.5	Asymptomatic	L-T4	No	157 20.6	6.8
	3-1	F	1.1	Asymptomatic	None	No	73 (-1.09) 19.1 (1.58)	8.57
4	2-2	F	40	Asymptomatic	None	No	155 36.6	7.9
	3-1	F	16.9	Asymptomatic	None	No	152 (-1.82) 25.3 (1.4)	5.5
5	2-1	M	36	Asymptomatic	None	No	170 24.2	7.8
	2-3	M	43	Asymptomatic	Propranolol	No	170 20.7	5.51
	3-1	M	6	ADD, LD	Propranolol	No	108.5 (-1.45) 12.4 (-2.64)	6.6
	3-2	M	11	Asymptomatic	None	No	143 (-0.15) 25.4 (1.8)	9.47
6	2-1	F	9.5	Anxiety disorder	None	No	137.7 (0.47) 20.4 (1.27)	7.43
7		F	20.5	Palpitation	Propranolol	Yes	160 23.4	8.6
8		F	53	Asymptomatic	NA	No	NA	5.62

Table 1. Continued

Family no	FT4 ng/dL (adult: 0.89-1.76) (children: 0.83-1.43)	TSH mU/L (0.5-4.78)	Autoimmunity markers	Thyroid volume (SDS or mL)	Thyroid nodule	Pituitary MRI	Other clinical features
1	NA	NA	NA	NA	NA	No	NA
	1.74	0.72	NA	NA	NA	No	(-)
	1.6	5.4	Anti-TPO + Anti Tg-	13.1 mL	Multinodular	No	(-)
	1.98	1.4	Anti-TPO + Anti-Tg +	2.3 SDS	No	No	(-)
	2.7	1.3	Negative	2.2 SDS	No	No	(-)
	1.9	1.8	Negative	-0.15 SDS	No	No	(-)
	1.9	4.1	Negative	1.1 SDS	No	No	(-)
	1.7	1.6	Negative	2.1 SDS	No	No	(-)
2	2.45	2.81	Negative	NA	Total thyroidectomy papiller thyroid cancer	No	Type 2 DM
	1.95	5.52	Negative	NA	Total thyroidectomy papiller thyroid cancer	No	(-)
	NA	NA	NA	NA	NA	No	NA
	1.98	3.1	Negative	NA	Total thyroidectomy benign multinodular goitre	No	(-)
	2.2	3.8	Negative	9.8 SDS	No	No	(-)
	2.1	3.3	Negative	2.64 SDS	No	No	(-)
	2.5	1	Anti-TPO + Anti-Tg +	9 SDS	No	No	(-)
	2.2	2.5	Negative	1.1 SDS	No	No	(-)
	2.6	3.9	Negative	2 SDS	No	No	(-)
	2.4	3.3	Negative	2.5 SDS	No	No	(-)
3	2.68	3.2	Negative	NA	Multinodular, FNAB recommended	No	(-)
	2.7	5.8	Negative	NA	No	Yes, normal	(-)
	2.54	3.6	Negative	1 SDS	No	No	Premature
4	2.7	7.9	Anti-TPO + Anti-Tg +	18.7 mL	Multinodular FNAB: Benign	Yes, microadenom	(-)
	2.6	2.4	Anti-TPO + Anti-Tg +	5.8 SDS	No	No	(-)
5	2.8	2.6	NA	NA	NA	No	(-)
	2.57	1.75	Negative	NA	No	Yes, normal	(-)
	2.7	2	Negative	1.8 SDS	No	No	Type 1 DM
	2.79	3.9	Negative	1.68 SDS	No	No	(-)
6	2.13	2.96	Negative	1.17 SDS	No	No	(-)
7	4	3	Negative	NA	No	No	NA
8	2.26	7.9	Anti TPO + Anti Tg-	NA	Multinodular	Yes, normal	NA

Age at dx: age at diagnosis, SDS: standard deviation score, NA: not available, BMI: body mass index, FNAB: fine-needle aspiration biopsy, FT3: free triiodothyronine, FT4: free tetraiodothyronine, TSH: thyroid-stimulating hormone, Mmz: methimazole, LT4: levothyroxine sodium, Anti-TPO: antithyroid peroxidase, Anti-Tg: anti-thyroglobulin, DM: diabetes mellitus, MRI: magnetic resonance imaging, ADD: attention-deficit disorder, LD: learning disability, F: female, M: male

Twenty-six patients with a pathogenic or likely pathogenic variant could be evaluated for autoimmune thyroiditis. Six (from four different families) (23.1%) of 26 patients had autoimmune thyroiditis. Of these, all were female. There was no significant difference between TSH (p = 0.466), fT4 (p = 0.420), and fT3 (p = 0.168) levels of patients with negative or positive thyroid autoantibodies.

Table 2. *THRB* gene variants detected in the families and variant classification according to the guidelines

Family	Mutation (cDNA/protein)	Cluster region/ domain	Status	ACMG classification	Inheritance
1	c.959G > A (p.R320H)	2	Clinvar-RCV000760097	Pathogenic; PS3, PM5, PM1, PM2	Familial
2	c.701C > A (p.A234D)	3	Reported by literature (43)	Likely pathogenic; PM5, PM1, PM2, PP3	Familial
3	c.794A > T (p.D265V)	3	Novel	Likely pathogenic; PM1, PM2, PP3-S	Familial
4	c.1291A > C (p.I431L)	1	Novel	Likely pathogenic; PM5, PM1, PM2, PP3	Familial
5	c.939G > A (p.M313I)	2	Novel	Likely pathogenic; PM5, PM1, PM2, PP3	Familial
6	c.749T > C (p.I250T)	3	Clinvar-RCV000760094	Likely pathogenic; PM1, PM2, PP3, PP5-M	*de novo*
7	c.1012C > T (p.R338W)	2	Clinvar-RCV000013385	Pathogenic; PS3, PM1, PM2, PP3-S	Unknown
8	c.980C > A (p.T327N)	2	Clinvar-RCV000582153	Likely pathogenic, PM1, PM2, PP3-S, PP5	Unknown

ACMG: American College of Medical Genetics and Genomics

Table 3. Comparison of the anthropometric and laboratory findings of the patients with a variant and without a variant but having clinical/laboratory findings similar to RTHβ

	Children *THRB* +	Children *THRB*-	p value	Adult *THRB* +	Adult *THRB*-	p value	All group variant +	All group variant-	p value
Female/male	11/5	3/4	0.363$^{\phi}$	7/7	2/8	0.210$^{\phi}$	18/12	5/12	0.044*
Age (year)	9.7 (5.2-11.4)	9.5 (8.3-11.9)	0.664$^{\Psi}$	36 (33.8-46)	27 (22.6-45.5)	0.253$^{\Psi}$	17 (9.1-36)	18.4 (10.4-33.5)	0.690$^{\Psi}$
Height SDS	-0.34 ± 0.91	0.32 ± 1.28	0.245$^{\mu}$	164.50 ± 9.85	NA	NA	NA	NA	NA
BMI SDS	-0.19 ± 1.49	0.11 ± 1.00	0.564$^{\mu}$	26.96 ± 6.15	NA	NA	NA	NA	NA
FT3	7.99 ± 1.38	6.17 ± 1.25	**0.009$^{\mu}$**	6.40 ± 1.39	5.40 ± 1.22	0.099$^{\mu}$	7.31 ± 1.58	5.74 ± 1.25	**0.001$^{\mu}$**
FT4	2.32 ± 0.34	1.87 ± 0.15	**0.004$^{\mu}$**	2.46 ± 0.64	2.07 ± 0.26	0.088$^{\Psi}$	2.38 ± 0.48	1.98 ± 0.25	**0.002$^{\Psi}$**
TSH	2.68 ± 1.04	2.23 ± 0.50	0.287$^{\mu}$	4.06 ± 2.28	1.95 ± 0.80	**0.016$^{\mu}$**	3.27 ± 1.79	2.07 ± 0.68	**0.014$^{\Psi}$**
Autoimmunity	3	0	NA	3 (33.3%)	1 (12.5%)	0.576$^{\phi}$	6 (24%)	1 (6.7%)	0.224$^{\phi}$
Thyroid SDS	2.87 ± 2.83	0.15 ± 0.58	**0.02$^{\Psi}$**	NA	NA	NA	NA	NA	NA
fT4/TSH	1.03 ± 0.54	0.87 ± 0.20	0.894$^{\Psi}$	0.87 ± 0.63	1.26 ± 0.68	0.136$^{\Psi}$	0.96 ± 0.57	1.09 ± 0.55	0.242$^{\Psi}$
fT4/fT3	2.96 ± 0.67	3.16 ± 0.91	0.662$^{\Psi}$	3.88 ± 0.67	4.20 ± 1.21	0.859$^{\Psi}$	3.35 ± 0.80	3.74 ± 1.18	0.479$^{\Psi}$
fT3/fT4	0.35 ± 0.06	0.33 ± 0.07	0.635$^{\mu}$	0.27 ± 0.05	0.26 ± 0.05	0.905$^{\mu}$	0.31 ± 0.07	0.29 ± 0.07	0.386$^{\mu}$

*Chi-square test, $^{\phi}$Fisher's exact test, $^{\mu}$Student's t-test, $^{\Psi}$Mann-Whitney U test. Data are presented as mean ± SD, or median (Q1-Q3).
BMI: body mass index, SDS: standard deviation (SD) score, NA: not available, fT3: free triiodothyronine, fT4: free tetraiodothyronine, TSH: thyroid-stimulating hormone, RTHβ: resistance to thyroid hormone β

Table 4. Comparison of the anthropometric and laboratory findings of the patients with a detected variant of RTHβ and healthy controls

	Children *THRB* +	Children control	p value	Adult *THRB* +	Adult control	p value
Female/male	11/5	14/10	0.505*	7/7	9/14	0.517*
Age (year)	9.7 (5.2-1.4)	9.4 (5.6-11.1)	0.945$^{\Psi}$	36 (33.8-46)	35 (25-43)	0.316$^{\Psi}$
fT3	8 ± 1.38	3.94 ± 0.22	**< 0.001$^{\mu}$**	6.41 ± 1.40	3.51 ± 0.38	**< 0.001$^{\mu}$**
fT4	2.32 ± 0.35	1.13 ± 1.12	**< 0.001$^{\mu}$**	2.46 ± 0.64	1.18 ± 0.15	**< 0.001$^{\mu}$**
TSH	2.69 ± 1.05	2.88 ± 1.2	0.605$^{\mu}$	4.07 ± 2.29	1.89 ± 1.00	**0.002$^{\Psi}$**
fT4/TSH	1.03 ± 0.54	0.45 ± 0.16	**< 0.001$^{\Psi}$**	0.88 ± 0.63	0.78 ± 0.35	0.972$^{\Psi}$
fT4/fT3	2.96 ± 0.67	2.89 ± 0.34	0.868$^{\Psi}$	3.88 ± 0.67	4.36 ± 0.63	0.053$^{\mu}$
fT3/fT4	0.35 ± 0.06	0.35 ± 0.04	0.877$^{\mu}$	0.27 ± 0.05	0.30 ± 0.04	0.054$^{\mu}$

*Chi-square test, $^{\mu}$Student's t-test, $^{\Psi}$Mann-Whitney U test. Data are presented as mean ± SD and (median (Q1-Q3).
fT3: free triiodothyronine, fT4: free tetraiodothyronine, TSH: thyroid-stimulating hormone, RTHβ: resistance to thyroid hormone β, SD: standard deviation

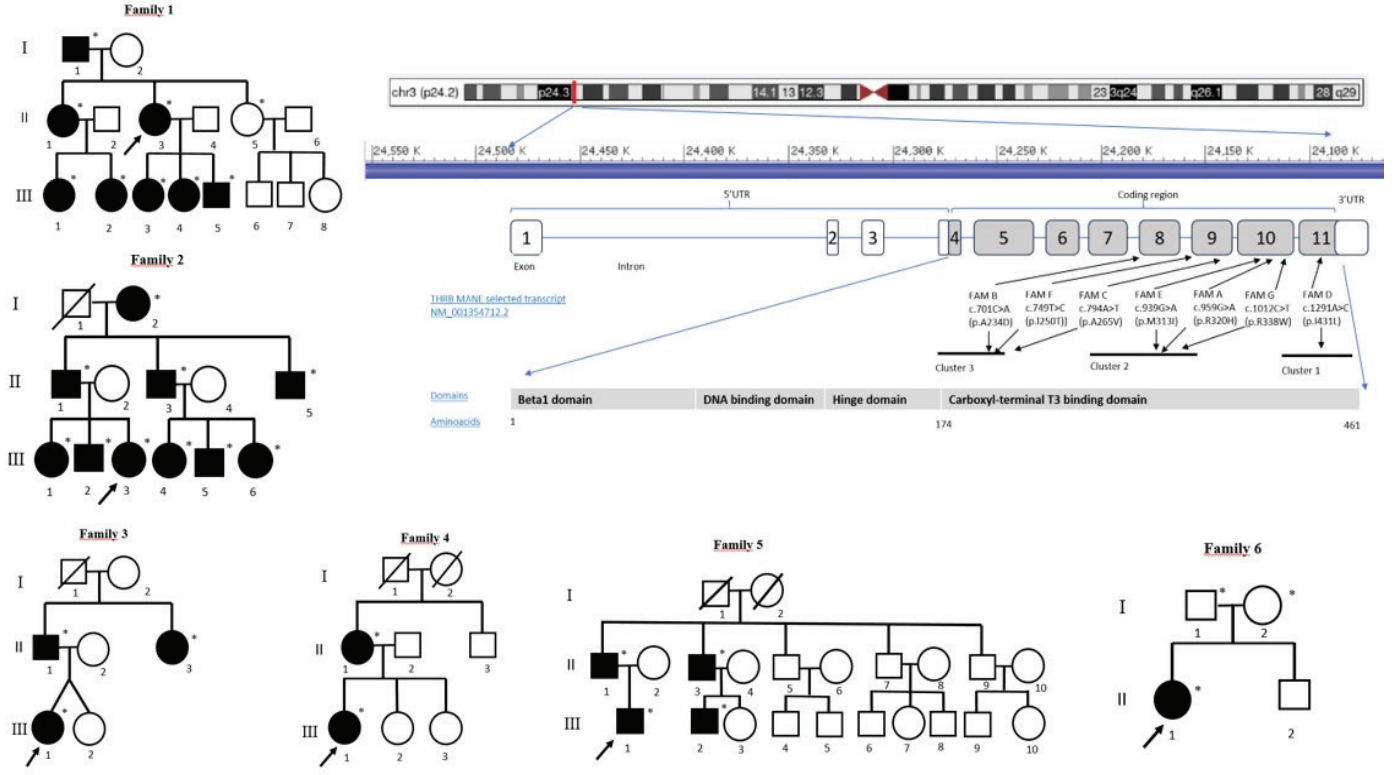

Figure 1. Schematic presentation of the chromosomal location, exon-intron organization, and protein domain content of the *THRB* gene. The detected variants have been aligned on the exonic and cluster levels. On the pedigrees of familial cases; black-filled squares and circles indicate affected individuals, and those marked with an asterisk indicate individuals with *THRB* gene analysis

In the RTHβ group, thyroid volume was above 2 SDS in 9/16 (56.25%) children. Furthermore, thyroid nodules were found in 7/14 (50.0%) adult patients. In one patient (2-2 from family 4), a fine-needle aspiration biopsy revealed benign cytology. In family 2, three individuals (1-2, 2-1, and 2-5) underwent total thyroidectomy. Of those two, (1-2 and 2-1) had papillary thyroid carcinoma (PTC) while patient 2-5 had a benign cytology result (21). A pituitary MRI, performed in four adult patients with a pathogenic or likely pathogenic variant, revealed pituitary incidentaloma in one and normal MRI in three patients.

A total of eight different heterozygous variants were detected in eight families. Three of these variants were novel. All variants were missense type resulting from a single nucleotide change. Three variants were in Cluster 3, four in Cluster 2, and only one in Cluster 1.

No variant was detected in the *THRB* gene in 20 patients. While 17 of the 20 patients were examined because of clinical and/or laboratory findings suggesting RTHβ, the remaining three euthyroid individuals were examined as part of family screening. Clinical characteristics and hormonal features of 17 patients (8 children, 9 adults) who underwent genetic analysis but no variant was detected are shown in Supplementary Table 1. Of the 17 patients without a variant, 16 were assessed for autoimmune thyroiditis. Out of these 16 patients, only one (7%) adult female had evidence of autoimmunity. The thyroid volume could be calculated in all children but in only seven/nine or 7/9 adult patients with no variant. In the pediatric group, thyroid volume was above 2 SDS in three children (37%), whereas 4/7 adults (57%) had goitre. Out of nine adult patients, seven underwent an cranial MRI scan. In one patient, a TSH-producing pituitary adenoma (TSHoma) was detected, while in another patient, a nonfunctional adenoma (incidentaloma) was detected. Since there was no Multiplex Ligation-dependent Probe Amplification kit available for *THRB*, two patients without detected variants underwent high-resolution array comparative genomic hybridization (CytoScan HTCMA_96r3.1, Thermo Fisher Scientific, Waltham, MA, USA). No pathology was detected.

Comparison of the anthropometric and laboratory findings of patients with a variant (n = 30) and without a variant, but having clinical/laboratory features of RTHβ (n = 17), are summarized in Table 3. In the pediatric group, patients

with a variant had significantly higher fT4 (p = 0.004) and fT3 (p = 0.009) levels than the variant-negative group, while no difference was observed in TSH levels (p = 0.287). Remarkably, in the adult group, while there was no significant difference between fT3 (p = 0.099) and fT4 (p = 0.088) levels of patients with and without variants, TSH levels were higher in patients with variants compared to the patients without variants [(4.06 ± 2.28 mIU/mL vs. 1.95 ± 0.80 mIU/mL), p = 0.016]. In addition, there was no difference between the fT4/TSH, fT4 (pmol/L) / fT3 (pmol/L), and fT3 (pmol/L) / fT4 (pmol/L) ratios of patients with or without a variant (Table 3).

Comparison of the laboratory findings of patients with a variant and a healthy control group are summarized in Table 4. There was no difference between TSH values in children. However, TSH levels were higher in adults with a variant. In addition, while the fT4/TSH ratio was higher in children with a variant, no difference was detected between the fT4 (pmol/L) / fT3 (pmol/L) (children, p = 0.868; adult, p = 0.053) and fT3 (pmol/L) / fT4 (pmol/L) ratios (children, p = 0.877; adult, p = 0.054) between the patients with a variant and healthy controls.

A comprehensive cardiological evaluation was performed for all pediatric patients regardless of variant status. No abnormalities were found on either echocardiography or electrocardiography of the patients, including holter monitoring performed in nine children.

Discussion

In the present study, evaluating *THRB* gene analysis in a series of 50 patients with signs and symptoms of RTHβ syndrome or a history of the index case in their families, eight *THRB* variants, of which three were novel, were detected in 30 out of 50 individuals.

Clinical manifestations of RTHβ syndrome vary widely. Although euthyroidism may be present in most patients with high TH values which are sufficient to stimulate the mutated receptors in most tissues, the phenotypes of the patients vary depending on the location of the hormonal resistance (9). The most common symptoms reported in the literature are goitre (65-85%), tachycardia (33-75%), attention-deficit/hyperactivity disorder and LD (33-68%), respectively (8,22,23). Less commonly reported symptoms were increased incidence of speech disorder, short stature, increased frequency of ear, nose, and throat infections, underweight in children, hearing loss, and cardiac abnormalities (23). In the present series, most of patients with a pathogenic or likely pathogenic variant were asymptomatic, consistent with the literature. RTHβ syndrome due to single amino acid changes in the *THRB* gene is reported to be milder than those due to insertion, deletion, or truncation variants (8,24). In our series, all patients with a pathogenic or likely pathogenic variant had missense heterozygous variants and we therefore attributed the high rate of asymptomatic cases to the universal presence of missense variants as the underlying molecular genetic etiology.

In a study evaluating RTHβ patients, 41.7% of the patients were reported to have received inappropriate treatments, including antithyroid therapy, thyroidectomy and radio-iodine ablation (25). While treatment is recommended for symptomatic cases, except for limited experiences with TH analogues (triiodothyroacetic acid, TRIAC), there is no specific treatment option for patients with RTHβ syndrome (26,27). Nevertheless, the rate of inappropriate treatment was decreased in the present study compared to previous publications, which may be attributed to the increased awareness of RTHβ and the opportunity to access molecular genetics analysis.

The increased prevalence of goitre despite mostly normal TSH has been reported to be due to alterations in terminal sialic acid residues, which enhance the biological potency of TSH (28). In our series, diffuse goitre was more prevalent in pediatric patients with a variant (56%) than in patients without a variant (37%).

TSHoma was detected in one of 17 patients with clinical/laboratory findings of RTHβ whilst no variants were detected in the *THRB* gene. There was no identified cause in the remaining 16 patients. The inability to explore the underlying etiology in these patients might be due to several factors, such as lack of facility to conduct further investigations and genetic analyses, errors in laboratory tests, the possible presence of somatic mosaicism, the existence of variants not covered by coding region sequencing, such as deep intronic variants, variants in inter- or intra-genic regions that regulate gene expression, or may be due to new modifier genes that has not yet been identified (1,4). Indeed, mosaicism in RTHβ was first reported by Mamanasiri et al. (29) who did not detect a variant in the *THRB* gene in 15% of individuals who had the RTHβ phenotype. Lack of measurement of serum biomarkers of TH effects on peripheral tissues, such as cholesterol, creatine kinase, alkaline phosphatase, osteocalcin and sex hormone binding globulin may be considered a limitation of our study. However, Refetoff et al. (3) reported that these values are less reliable unless measured before and after administration of T3.

The number of studies comparing patients with and without RTHβ is scarce. In the study of Brucker-Davis et al. (23), individuals with RTHβ were younger, exhibited a higher rate

of palpable goitre, had shorter stature, lower body weight, lower IQ scores, higher fT3 and fT4 levels, and higher T4/TSH and T4/T3 ratios. In the present series, in children with a variant, fT3 and fT4 values were higher than those without variants, while in the adult group, no differences were observed in these values. Furthermore, fT4/TSH, fT4/fT3, and fT3/fT4 ratios of patients with and without a variant did not differ. Compared to healthy controls, TSH levels were not different in children but were higher in adults with a variant. Moreover, the fT4/TSH ratio was higher in children with a variant whilst no difference was detected between the fT4/fT3 and fT3/fT4 ratios. This finding was consistent with the results of Refetoff et al. (3) indicating the total T3/total T4 ratio of patients with generalized RTHβ was only slightly above the mean value found in euthyroid-healthy individuals.

Individuals with RTHβ have been reported to have a higher likelihood of developing autoimmune thyroid disease (AITD) (30). In the present study, the rate of AITD was 23% in RTHβ and all cases were female which was consistent with the previously reported female predominance (25). While Gavin et al. (31) suggest that high TSH in RTHβ might activate intrathyroidal lymphocytes and increase proinflammatory cytokines and thyroid cell destruction, Barkoff et al. (30) reported that this hypothesis does not explain the increased autoimmunity in RTHβ. Moreover, the role of TH on the immune system is still poorly understood, and TH is reported to activate the immune system by acting directly on thymic epithelial cells, neutrophils, natural killer cells, macrophages, and dendritic cells (9,32,33). Besides, while there is a well-known female predominance in thyroid autoimmunity, there is no sex difference in RTHβ. However, all patients with thyroid autoimmunity were female in our series and some of the other studies suggest a need for further investigation of the mechanism behind the association between AITD and RTHβ which remains unclear.

RTHβ has been reported in patients with renal failure, ichthyosis-eczema, psychotic attacks, oesophagal atresia, reflux, celiac disease, congenital heart disease, and T1DM and T2DM (23,26,34,35). One patient in our series was also diagnosed with T1DM. TRs such as TRα1 and TRβ1 have been shown to be expressed in pancreatic beta cells (36). In addition, it has been reported that T3 induces the proliferation of pancreatic β-cells by activating phosphoinositide 3-kinase/Akt kinase pathways. Therefore, T3 could be considered a survival factor for islet cells, by protecting them from apoptosis (37). Except for the single case in our series, T1DM has only been reported in two other cases. There is insufficient evidence to consider whether this association was coincidental or not. Although the results of studies evaluating the effects of TH on insulin secretion are controversial, the effect of mutant TH receptors on islet cell function is not fully understood, and assessment of glucose metabolism in these patients is warranted (38,39).

Studies investigating the role of TH receptors in cancer have argued that decreased TR gene expression in cancer tissues due to hypermethylation or TR gene deletions can be explained by the potential tumour-suppressive function of TRs. Furthermore, these studies have highlighted the association of somatic variants in TRs with human cancers, suggesting that the loss of normal TR function might lead to uncontrolled cell growth and poor differentiation (40). In 2001, Taniyama et al. (41) reported the first case of RTHβ associated with PTC. In 2022, Fang et al. (42) published a literature review of 17 cases including their case. Two patients in Family 2 investigated in the present study were also reported in this series (21).

Study Limitations

Our study has some limitations. First, the sample size was relatively small. Due to the low frequency of RTHβ, further multicenter or nationwide studies with larger sample sizes are needed to elucidate the clinical characteristics and genotype-phenotype association of RTHβ. Second, in some patients, in whom we could not detect a *THRB* gene variant, further investigations using advanced genetic and laboratory analysis methods were not performed.

Conclusion

In conclusion, in the present study evaluating the clinical and genetic characteristics of a series of 30 Turkish patients with genetically confirmed RTHβ, the *THRB* gene variant database was expanded by the addition of three novel variants. Moreover, our results provide insights into prioritizing individuals for genetic analysis by comparing RTHβ patients with and without a variant. Although most patients with RTHβ are asymptomatic, prompt molecular genetic analysis for *THRB* gene variants and regular follow-up for potential concurrent autoimmune diseases and thyroid cancer is warranted.

Ethics

Ethics Committee Approval: The study was approved by the Clinical Research Ethics Committee of Ankara Bilkent City Hospital with decision number: 23-5676, date: 22.11.2023.

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

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