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Clinical Research Article

Clinical and Biochemical Characteristics of Untreated Adult Patients With Resistance to Thyroid Hormone Alpha

Louise Koren Dahll,[1] Alexander Bauer Westbye,[1] Kristin Vinorum,[2] Yngve Sejersted,[2] Tuva Barøy,[2] Per Medbøe Thorsby,[1,3] and Sara Salehi Hammerstad[3,4,5]

[1]Hormone Laboratory, Department of Medical Biochemistry and Biochemical Endocrinology and Metabolism Work Group, Oslo University Hospital, Oslo 0424, Norway
[2]Department of Medical Genetics, Oslo University Hospital, Oslo 0424, Norway
[3]Institute of Clinical Medicine, University of Oslo, Oslo 0316, Norway
[4]Department of Endocrinology, Oslo University Hospital, Oslo 0424, Norway
[5]Department of Pediatric Medicine, Oslo University Hospital, Oslo 0424, Norway

Correspondence: Louise K. Dahll, MD, The Hormone Laboratory, Department of Medical Biochemistry, Oslo University Hospital, Postboks 4950, Aker sykehus, Nydalen, Oslo 0424, Norway. Email: lokoda@ous-hf.no.

Abstract

Background: Thyroid hormone resistance due to pathogenic variants in thyroid hormone receptor alpha (*THRA*) is rare and descriptions of patients are sparse. The disorder is probably underdiagnosed as patients may have normal thyroid function tests. Treatment with thyroxine in childhood improves clinical symptoms. However, it is not clear if treatment has beneficial effects if started in adulthood.

Cases: We investigated 4 previously untreated Caucasian adult first-degree-related patients with the *THRA* c.788C > T, p.(Ala263Val) variant identified by a gene panel for intellectual disability in the index patient. Clinical data and previous investigations were obtained from medical reports.

Results: During childhood and adolescence, short stature, short limbs, metacarpals, and phalanges, and delayed bone age maturation were observed. Delayed motor and language development and decreased intellectual and learning abilities were described. Abdominal adiposity, round face, and increased head circumference were common features. All individuals complained of tiredness, constipation, and low mood. While thyrotropin (TSH) and free thyroxine (FT4) were within the reference range, free triiodothyronine (FT3) was high. FT4/FT3 ratio and reverse T3 were low. Other main features were low hemoglobin and high LDL/HDL ratio.

Conclusion: Investigation of 4 first-degree-related adult patients with untreated resistance to thyroid hormone alpha (RTHα) revealed more pronounced phenotype features and hypothyroid symptoms than previously described in patients treated with levothyroxine from childhood or adolescence. The delay in diagnosis is probably due to normal thyroid function tests. We suggest that *THRA* analysis should be performed in patients with specific clinical features, as treatment in early childhood may improve outcomes.

Key Words: thyroid hormone, thyroid hormone receptor, *THRA*, short stature, obesity

Abbreviations: BH, birth height; BMI, body mass index; BW, birth weight; FT3, free triiodothyronine; FT4, free thyroxine; HDL, high-density lipoprotein; IGF-1, insulin-like growth factor 1; LBD, ligand-binding domain; LDL, low-density lipoprotein; RTHα/β, resistance to thyroid hormone alpha/beta; T3, triiodothyronine; T4, thyroxine; THRA, thyroid hormone receptor alpha; TR, thyroid hormone receptor; TSH, thyrotropin (thyroid stimulating hormone).

Thyroid hormones are important regulators of growth and development, metabolic rate, energy homeostasis, heart and bowel function, central nervous system maturation and cholesterol conversion. The *THRA* and *THRB* genes encode thyroid hormone receptors (TR), both producing multiple isoforms through alternative splicing. The isoforms TRβ1, TRβ2 and TRα1 bind triiodothyronine (T3) while TRα2 does not bind T3 but acts as an inhibitor by competing for DNA [1, 2]. These nuclear receptors, found in most cells, form monomers, homodimers, or heterodimers with retinoid X receptors at DNA binding sites on target genes (thyroid hormone-responsive elements) and mediate gene regulation by binding of T3 [3, 4].

Pathogenic variants in the receptors are rare but can cause disease due to cellular resistance to T3. The clinical symptoms are receptor specific, because TRα and TRβ are unevenly distributed in the tissues. TRα is the predominant receptor in the central nervous system (CNS), intestines, bone, and cardiac and skeletal muscle, while TRβ is predominant in the hypothalamus, pituitary, retina, cochlea, thyroid gland, liver, and kidneys [5, 6].

Pathogenic variants in *THRB* causing resistance to thyroid hormone beta (RTHβ) are suspected if the patient has normal or slightly elevated thyroid stimulating hormone (TSH) and elevated tetraiodothyronine (T4) and freeT4 (FT4). Heterozygous pathogenic variants in *THRA* are associated

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with resistance to thyroid hormone alpha (RTHα), causing autosomal dominant nongoitrous congenital hypothyroidism. The receptor translated from the alternative allele causes thyroid hormone resistance by inhibiting wild-type receptor action in a dominant negative manner.

The pathogenic *THRA* variants described so far are most frequently located in the C-terminal ligand-binding domain (LBD) [2, 7]. Nonsense, frame shift, and missense variants close to the C-terminus appear to lead to more severe phenotypic features than missense variants located in the more N-terminal gene segment common to the TRα1 and TRα2 isoforms. A key molecular pathogenic defect may be persistent co-repressor binding, rather than coactivator recruitment per se. The variants associated with the most severe outcomes do not only prevent T3-binding but also coactivator recruitment [8-11]. The p.(Ala263Val) variant is located in the N-terminal segment of the LBD common to the TRα1 and TRα2 isoforms. This variant is found to cause reduced affinity for T3 which in vitro is overcome by high doses of T3 [12]. Phenotypic variation between patients, and also between family members with the same pathogenic variant in *THRA* has been reported [13].

Here we report available clinical and laboratory characteristics from childhood and onwards of 4 previously untreated adult patients with RTHα. These descriptions may aid pediatricians to identify the disease in patients at an early age.

Material and Methods

A father and his 3 adult children, 2 daughters and a son, were referred from the genetic department to the outpatient thyroid clinic at Oslo University Hospital in 2018 for assessment. All 4 had the *THRA* c.788C > T, p.(Ala263Val) variant and had not previously received treatment. The index patient was referred to the genetic department at the age of 15 due to clinical features and was diagnosed with RTHα at the age of 18. The children's mother did not present the gene variant and volunteered as a control.

This study was approved by the Institutional Review Board and the Norwegian Regional Committee for Medical and Health Research Ethics (REK). Written informed consent was obtained from all family members.

Medical Records, Clinical Features

Information regarding clinical descriptions, developmental tests, milestones, symptoms of hypothyroidism, and a family history for preparing a pedigree are based on medical records and investigations at admission to the outpatient thyroid clinic.

Genetic Investigation

Molecular genetic analyses using genomic DNA from the index patient was initiated at age 13 and included a chromosomal microarray (SurePrint G3 Human Exon 4 × 180k Microarray Kit, Agilent Technologies), Sanger sequencing of *NSD1*, *SHOX*, *PTEN*, and *PTEN* promotor and multiplex ligation dependent probe amplification of *SHOX* and *PTEN* (MRC Holland P026 and P018).

At age 18, a diagnostic in silico gene panel for intellectual disability containing 849 genes (Supplementary Table S1) [14] was analyzed (Gene sequences were obtained using SureSelect Human All Exon v5 exome kit (Agilent Technologies), and a HiSeq2500 sequencer (Illumina). Variants with global allele frequency >1% in ExAC [15] or 1000 genomes [16], or >5% in local in-house databases, were removed. Of the remaining variants, only a heterozygous variant in *THRA* (NM_199334.3): c.788C > T, p.(Ala263Val) (chr17(GRCh37):g.38244559C > T) was suspected to be disease-causing.

Biochemical Investigation: Thyroid Function Tests

Morning blood samples after an overnight fast were collected, centrifuged, and analyzed shortly after retrieval at the Hormone laboratory, Oslo University Hospital using available commercial kits. TSH (reference range, 0.5-3.6 mU/L) was measured with noncompetitive immunofluorometric analysis by Autodelfia (Wallac Oy, Turku, Finland- RRID: AB_2877703). FT4 (8.0-21.0 pmol/L) was measured with solid-phase time-delayed fluoro-immunoassay with back-titration by Autodelfia (Wallac Oy, Turku, Finland- RRID: AB_2801661). FT3 (2.8-7.0 pmol/L) was measured with competitive electrochemiluminescence immunoassay by Cobas e601 (Roche Diagnostics, Indianapolis, IN, USA AB_2827368). Reverse T3 was analyzed using a competitive RIA (DIAsource ImmunoAssays S.A, Belgium).

Sex hormone–binding globulin (SHBG), thyroxine binding globulin (TBG), and insulin-like growth factor 1 (IGF-1) using a chemiluminescent immunometric assay (Siemens IMMULITE 2000, Siemens). Androstenedione was analyzed using liquid chromatography tandem mass spectrometry (LC-MS/MS Agilent, 1290 UHPLC coupled to a 6490 triple quadrupole MS) by a method developed at the Hormone laboratory. Cholesterol, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) were measured as routine analyses at Oslo University Hospital.

Developmental Tests

Information regarding clinical development is based on medical records and investigations on developmental assessments performed with Leiter-R, Wisc-R, and ITPA-test [17-19].

Results

Characteristics

The family pedigree is shown (Fig. 1A). The participants' characteristics and photographic images are presented (Table 1 and Fig. 2, respectively). Heart rate and blood pressure were normal for the 3 siblings, while the father had elevated systolic and diastolic blood pressure. All 4 patients were overweight, were of short stature and had short limbs. Growth curves for patient 4 are presented in Supplementary Fig. S1A and S1B [20] (percentiles from [21, 22]).

Laboratory Assessment

The variant was confirmed by Sanger sequencing in the index patient (Fig. 1B) and found to co-segregate with the disease in 3 affected and 4 unaffected family members. The variant altered an evolutionary conserved amino acid, and no amino acid substitutions affecting codon 263 were present in the Genome Aggregation Database (v2.1.1 and v3.1.2).

Thyroid function tests showed normal TSH and FT4 (Table 2). FT3 levels were just below the upper reference range or slightly elevated in all the patients. In all 4 patients, FT4/FT3 ratio was lower compared with both healthy controls

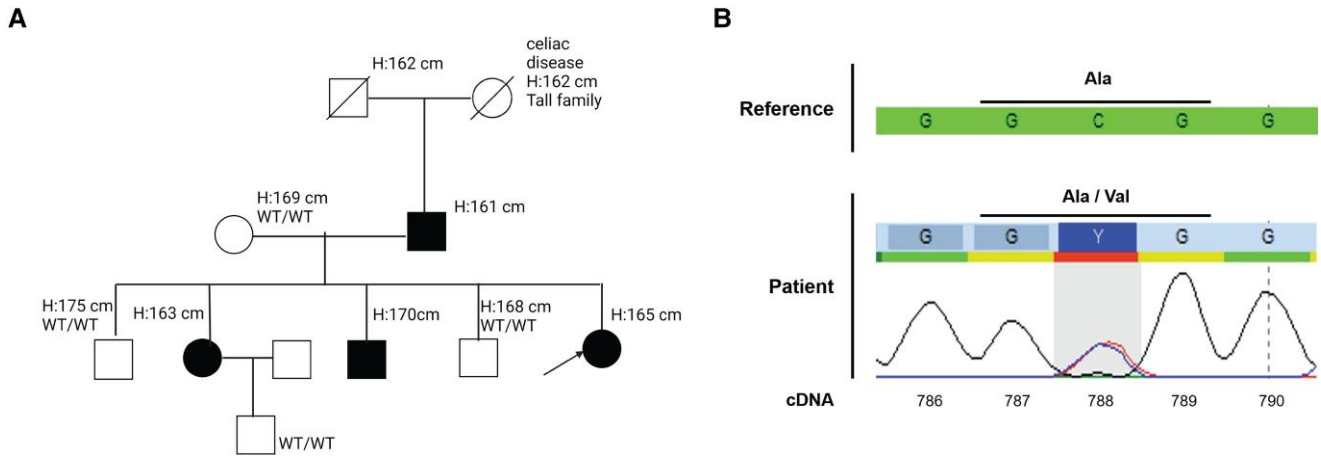

Figure 1. (A) Pedigree of the affected family. Molecular analysis of the index patient (arrow), her parents, siblings, and nephew. Black squares/circles indicate individuals confirmed to have the nucleotide substitution (c.788C > T) corresponding to an alanine to valine substitution at codon 236. Family members with confirmed normal THRA variants are indicated WT/WT. Pedigree created with Biorender.com. (B) Sanger sequencing of *THRA*. Sanger sequencing chromatogram of *THRA* (index patient). The heterozygous c.788C > T, p.(Ala236Val) variant is shown.

without any thyroid diseases and anonymized reference values from our laboratory (negative thyroid peroxidase antibodies TPO-Ab] and thyrotropin-receptor antibodies [TRAb], and TSH within the reference range), regardless of age (Fig. 3 and Table 2). Similarly, rT3 levels were lower than the reference range (Table 2).

Hemoglobin below or in the low normal reference range was a common feature in all participants regardless of age and sex. LDL levels were in the upper reference range and the LDL/HDL ratio was high. Fasting C-peptide was above the reference range in the 2 patients with the highest body mass index (BMI) (Table 3).

Clinical Description

The index patient

A female, the youngest of 5 siblings, was nearly 20 years old on admission to the thyroid outpatient clinic. She was born 2 weeks overdue. At birth, her mother immediately recognized the facial features and body composition of her husband and 2 of her children—later diagnosed with RTHα. Birth weight (BW) was 4.96 kg and birth height (BH) was 53 cm (median BW for girls in Norway is 3.6 kg [reference range, 95%: 2.7-4.6], and median BH 50.4 cm [reference range, 95%: 46.5-54.4]) [23]. Her mother had gestational diabetes mellitus. At delivery she presented with hypoglycemia and was treated with glucose intravenously. Lactose intolerance was detected when she was a toddler. Recurrent otitis media led to bilateral paracentesis at the age of 1 and adenotonsillectomy at age 6. She started walking at 13 to 14 months. She was short and had stout thighs and calves. Delayed language development was observed from 20 months.

She was tested with the Illinois Test of Psycholinguistic Abilities (ITPA) test at the age of 5 years and 8 months. Her average score was lower than the expected. She scored above the standard deviation in 2 of the visual tasks and below the standard deviation in 3 of the auditory tasks. She could pronounce "r" and learned to ride a bicycle when she was 8 years old. She had general learning difficulties, with a cognitive capacity in the lower normal range. From the age of 10 she received teaching support. She achieved normal grades at school and completed upper secondary vocational education.

During childhood and adolescence, she was often tired and had little energy to meet friends after school. She went to bed between 9 and 10 in the evenings and slept for 10 to 11 hours. At the age of 12 her skeletal age was normal, but micromelia (short metacarpals and phalanges) was recognized by the radiologist. When she and her 2 affected siblings were teenagers, they had to wear shoes that were 2 sizes too large because of abnormally wide feet. At that time she had normal thyroid function tests: TSH, 1.6 mmol/L (reference range [RR] 0.5-4.9), and FT4, 13 pmol/L (9-16). Repeated measurements after 2 years showed stable TSH and low normal FT4, 10 pmol/L. Due to short stature with short limbs, macrocephaly, and developmental delay, the *NSDI*, *SHOX*, and *PTEN* gene were analyzed with normal results. When she was 15 years old, she was referred to Oslo University Hospital for genetic counseling. By then she had developed pronounced truncal obesity with a BMI of 40 kg/m^2. She had a large round head, broad face, flat nasal bridge, a narrow palpebral fissure length, and short limbs. Her voice was nasal, and she spoke with a slight lisp. At the age of 18, analysis of a gene panel for intellectual disability disclosed the c.788C > T p.(Ala263Val) variant in *THRA*.

Upon admission to the thyroid outpatient clinic, she had a nasal voice and complained of tiredness and constipation, passing stool every third to fourth day. Compared to Norwegian 19-year-old females she was short and severely obese (Table 1) [30, 31]. Her head circumference was increased [23]. In contrast to a normal population [24], her limbs were short for her height (sitting height in the upper range) (Fig. 2D) and her arm span was shorter than her body height. She had broad hands, large feet and wore shoes 4 sizes larger than estimated from her body height [29].

Patient 2

The father was 64 years old at admission to the outpatient clinic. Based on information in the patient record, he was delivered 3 weeks overdue, with BW 3.2 kg and BH 49 cm (reference mean BW 3.5 kg [SD 0.57] and mean BH 50.9 cm [SD 2.7]) [32].

Table 1. Clinical and auxological characteristics

	Index patient	Patient 2	Patient 3	Patient 4	*Mother
Age (years)	19	64	26	25	60
Gender	F	M	F	M	F
Weight kg (ref. range)[a]	**119** (48-77)	97 (NA)	**155** (48-77)	**111** (57-101)	81.7 (NA)
Height cm (ref. range)[a,b]	165 (154-179)[a]	161 (177)[b]	163 (154-179)	170 (167-194)	165 (NA)
Arm span cm (ref. range)[c]	160 (166)	157 (162)	158.5 (164)	170 (171)	169 (166)
Sitting height cm (ref. range)[d]	88.6 (82-91)	88.6 (NA)	**90.1** (81-90)	91.8 (81-92)	82.8 (NA)
BMI kg/m^2 (ref. range)[e]	**43.8** (18-28)	**37.4** (27)	**58.0** (18-28)	**38.0** (17-30)	30.0 (26)
Head circumference cm (ref. range)[f]	**60.1** (52-58)	**63.0** (53-59)	**60.5** (52-57)	**61.0** (54-59)	54.5 (52-58)
Blood pressure mmHg (ref. range)[g]	122/**83** (94-136/ 47-80)	**170/114** (101-175/ 58-100)	118/79 (94-136/ 47-80)	127/82 (103-148/ 47-83)	126/83 (98-175/ 51-95)
Heart rate bpm (ref. range)[g]	57 (51-95)	72 (44-91)	65 (51-95)	68 (47-91)	83 (46-94)
Shoe size (continental) (predicted size based on height)[h]	**42** (38)	**42** (<39)	**42** (38)	**44** (41)	39 (38)

Values outside the reference ranges are marked in bold.
Abbreviations: BMI, body mass index; bpm, beats per minute; F, female; M, male.
[a]Reference ranges are extracted from available literature. Patient 3 and 4: Height, weight or BMI and range (± 2 SD) from Norwegian 19-year-olds [23].
[b]Patient 2 and mother: Mean height of Norwegian military conscripts (by year of birth) (Statistics Norway, table SY 108).
[c]Predicted arm span from height [24].
[d]Sitting height range (mean ± 2 SD) predicted from patient height [25]. Patient 3 and 4 predicted using ratios for age 21 years. Dutch population.
[e]BMI [26].
[f]Head circumference range (3rd to 97th percentile) of adult females and males [27]. British population.
[g]Systolic and diastolic blood pressure and heart rate range (calculated from mean ± 2SD) for the Norwegian HUNT3 (2006-2008) cohort [28]. Index patient compared to age group 20-29 years.
[h]Estimated shoe size by height [29] in parenthesis. Conversion of US Women's size to continental size based on a Nike size chart.
*Mother served as control.

The father started to walk at 16 months old, he said "mummy" when he was 1 year old but did not speak any other words until he was 3 years old. He was referred to the oral surgery department at the nearest University Hospital when he was 7 years old for extraction of 2 worn down (caries decayed) deciduous teeth. He was at this time described as a short, stout, nervous and anxious boy who had suffered from eczema, frequent colds, bronchitis, and otitis media. A big tongue and short thighs were observed. His speech was indistinct, he stuttered and could not pronounce "k" and "g" and was referred to a speech therapist. He received teaching support for 3 years from the age of 8.

At age 11, he was referred to the pediatric outpatient clinic at the nearest University Hospital for investigation of short stature and suspected hypothyroidism. At that time, he had anemia with hemoglobin 10.2 g/dL, and bone age maturation corresponding to 6 to 7 years. Insulin-glucose load, ACTH and metyrapone test, air encephalogram, hormonal pituitary examination, and other biochemical status were normal, and the investigation concluded with constitutional growth delay. Protein-bound iodine was in the low normal range and primary hypothyroidism was considered less likely. At this time (11 years) his height was 124.5 cm (8 cm below the 2.5 percentile), and he weighed 30.9 kg (about 2 kg above the 97.5 percentile in relation to height) [32].

At admission to the outpatient thyroid clinic, his appearance was stout with a round face, broad hands and feet, and short fingers. He had a large chest with numerous moles on his chest and back and some skin tags in the neck, abdominal obesity, and short extremities (Fig. 2D). Despite being physically active, his weight had gradually increased by 34 kg from when he was 23 years old. Cortisone injections were given each spring to treat hay fever and he took nasal spray for allergic rhinitis. He complained of tiredness, exhaustion, and low mood. He was shorter and more overweight than the average for Norwegian men of the same age (Table 1) [31, 33] and his head circumference was increased [23].

Patient 3

The older sister, (7 years older than the index patient) was first evaluated in the thyroid outpatient clinic when she was 26 years old. She was born after a normal pregnancy and had normal weight and height at delivery, BW 3.57 kg and BH 50 cm. She learned to walk without support when she was 19.5 months. Her language development was delayed and she could only utter some two-word sentences when she was 2 years old. As an infant and toddler, she was treated with hydrocortisone cream for atopic eczema. Due to obstructive episodes related to several upper respiratory tract infections she received inhalation therapy with salbutamol and budesonide.

Figure 2. Photographs of patients. (A) Patient 3:10 years old, (B) Patient 4: 7 years old, (C) Index patient: 3 years old, From left to right (D) Mother (unaffected), patient 3, patient 4, index-patient, patient 2 (father). Photo taken 4 years after admission. Note: elbows reach the middle of the ribcage.

At 5 years and 4 months she was referred to the local Educational and Psychological Counselling Service ("Pedagogisk psykologisk tjeneste"). The evaluation described a delay of 1.5 to 2 years in mental and intellectual function. Special education assistance was recommended in daycare and at school. From the age of 5, she was described as significantly overweight and was therefore examined in primary care when she was 9 years old. Blood tests showed TSH, 1.8 mIU/L (reference range, 0.35-5); FT4, 9 pmol/L (11-23); and FT3, 7.6 pmol/L (3.5-6.5). She had an iron sufficient microcytic anemia with an red blood cell count slightly below normal and hemoglobin of 11.2 g/100 mL (11.5-14,5). At age 11 her BMI was 34 kg/m^2 and she weighed 66.5 kg, 22.5 kg above the 97.5 percentile for height [23].

She attended a standard public school but had an individual education program. The third year of lower secondary school she attended a school specifically tailored to children with disabilities. She completed a vocational education at upper secondary level, but her school performance was in the lower half of the grading system. She was often tired and could fall asleep during daytime. Heavy sleeping forced her to use 5 alarm clocks to wake herself in the morning. When tested, her apnea-hypopnea index did not meet the criteria for obstructive sleep apnea. Borderline high level glycated hemoglobin (HbA1c) was detected when she was 21 years old, and 2 years later she presented with gestational diabetes.

Patient 3, along with her mother (who weighed 125 kg) and the index patient, were referred to a nutritionist and were

Table 2. Thyroid function test results

	Index patient	Patient 2	Patient 3	Patient 4	Mother[a]	Reference range
TSH	2.9	0.55	2	1.9	0.82	0.5-3.6 (mU/L)
FT4	15	13	9.6	9.6	19	8.0-21.0 (pmol/L)
FT3	**7.8**	6.2	6.8	**7.2**	3.8	2.8-7.0 (pmol/L)
FT4/FT3	**1.9**	**2.1**	**1.4**	**1.3**	5	See Fig. 3
rT3	**0.18**	**0.21**	**0.11**	**0.12**	0.28	0.26-0.69 (nmol/L)
TT4	125	118	86	84	92	60-150 (nmol/L)
TT3	**2.9**	2.4	2.8	**3**	1.3	1.2-2.8 (nmol/L)
TBG	22.6	15.6	17.5	20.3	19	14-31 (mg/L)

Results in bold show low FT4/FT3 ratio and high FT3.
Abbreviations: TSH, thyroid stimulating hormone; T3, triiodothyronine; T4, thyroxine; TBG, thyroxine binding globulin.
[a]The mother served as a control. Reference ranges (RR) for the mother at the local hospital were TSH: 0.27-4.2 mIU/L, FT4: 12-22 pmol/L, FT3: 2.6-5.7 pmol/L.

evaluated by an institution specializing in treatment of patients with morbid obesity. A change in diet and lifestyle was successful and they achieved significant weight loss. However, both patient 3 and the index patient soon regained weight to pretreatment levels in contrast to their mother, who sustained her weight loss of more than 40 kg.

On evaluation, patient 3 was obese, class 3. The investigation revealed numerous moles on her back, her thyroid was slightly enlarged with a firm nodule in the right lobe, about 10 mm in diameter. She complained of tiredness and periodically a lack of energy to meet friends, and had only capacity to perform housework 20 minutes a day. She had abdominal pain related to constipation and hard stool every third to fourth day. She used desogestrel contraceptives, and a beta 2 agonist (terbutalinsulfat) and budesonide for inhalation when obstructive.

Patient 4

The older brother (6 years older than the index patient) was 25 years old at admission. He was born after an uncomplicated pregnancy and delivery, BW 3.75 kg and BH 52 cm (median BW for boys in Norway is 3.7 kg [reference range, 95%: 2.8-4.6], median BH 50.7 cm [reference range, 95%: 46.5-54.9]) [23]. As a toddler, he was treated for atopic eczema and upper airway infections with hydrocortisone cream, beta 2 agonist (terbutalinsulfat), and budesonide. He had recurrent lung and ear infections and was treated with adenoidectomy and bilateral myringotomy when he was 4 years old.

At age 6 he was referred to the local pediatric ward for investigation of short stature. His height was 106.3 cm, 3 cm below the 2.5 percentile. Weight 22 kg, equivalent to the 97.5 percentile. His growth curve was followed regularly (Supplementary Fig. S1) [20] until he was 17 years of age at the local pediatric ward. His height was consistently below the 2.5 percentile and his weight gradually increased.

At age 7, his upper front teeth were worn down completely; he had speech impediments and hoarseness and was treated by a speech therapist. At the same age he was referred to an ophthalmologist because of stumbling over uneven terrain at the daycare center. He also complained of visual difficulties when solving puzzles. Visual examination showed only mild hyperopia, which was corrected with glasses for a few years until retesting of his vision revealed short-sightedness.

At age 8, he was investigated by neurologists at Oslo University Hospital, who concluded that he had delayed development of speech, delayed growth, and delayed psychomotor development. He was described as having narrow eye slits, a short philtrum, a thin upper lip, worn teeth, and stout calve muscles. At age 9, intellectual tests [17, 18] were not conclusive of mental retardation. The inquirer stated that his concentration problems probably negatively biased the test results. At age 13 years and 7 months, x-ray investigation revealed mesomelia (shortening of the forearms and lower legs) corresponding to the lower normal reference range for a child aged 11.5 years, while the humerus and femur were in the lower normal range for chronological age. Short metacarpals and phalanges were also observed. Blood tests performed at age 14 showed elevated FT3, 7.9 pmol/L (3.0-5.8) but normal TSH, 1.7 mIU/L (0.5-4.9); FT4, 13 pmol/L (9-16); and IGF-1, 20 nmol/L (19-130). He started school one year delayed with special educational facilitation. From lower secondary school he attended a school providing adapted education and completed a vocational education at upper secondary level.

At admission to the outpatient thyroid clinic he had abdominal obesity, increased head circumference [23, 30], a broad face and chest, broad hands and feet with short fingers and toes, a pigmented area on his back and upper abdomen, numerous moles and a few skin tags on his back and face (Table 1). His thyroid was barely palpable and without nodules. The patient complained of tiredness, he usually went to sleep at 11 PM, woke up at noon the next day, and had excessive daytime sleepiness. He could fall asleep for hours during the daytime when sitting down without anything to occupy him. He had problems with concentration, and information was retained only if repeated several times. He had always suffered from constipation, with hard stool every second day and straining when passing a stool. He used antihistamine for hay fever as needed and aripiprazole (Abilify) 400 mg every fourth week from 20 years of age for paranoid delusions.

The Mother (nonaffected family member) was 60 years old at admission. She has a history of gestational diabetes, cardiovascular disease, and fibromyalgia. She presented normal clinical characteristics, normal thyroid function, and normal biochemical findings except for lipoprotein(a) and HbA1c (Tables 1-3). All her children were born approximately 14 days overdue.

Discussion

In this paper we present the clinical and laboratory data of 4 first-degree-related patients with RTHα. RTHα is a rare

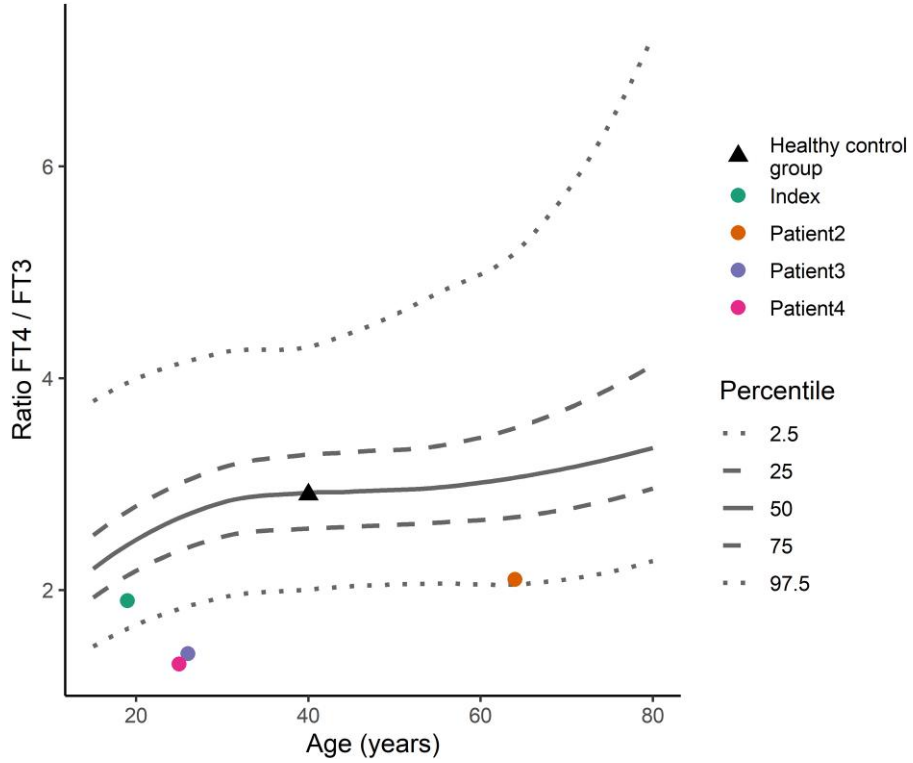

Figure 3. Distribution of FT4/FT3 ratio. Median calculated FT4/FT3 ratio by age group comparing patients to controls. Percentile distribution of FT4/FT3 ratios in presumed healthy patients was obtained by exporting data from 4.5 years of clinical routine production results. Anonymized data was filtered to remove likely pathologic results; patients with at least one positive TPO-Abs or TRAS, or a TSH outside the reference range, and patients that were analyzed more than once were removed. Results were grouped in 5-year age categories and percentiles calculated for each category. The healthy controls group consisted of 47 healthy individuals (mean age 40 years) (FT4/FT3 ratio range, 2.2-3.7).

genetic disease and this is the first family in Norway reported to have a pathogenic *THRA* variant.

Thyroid hormone resistance can be caused by variants in *THRB* or *THRA*. The incidence of RTHβ has been estimated to be 1:40 000 [34]; symptoms vary from asymptomatic to debilitating. Although RTHβ is rare, the condition is readily recognized due to elevated thyroid function tests with nonsuppressed TSH. The incidence of RTHα is unknown, as pathogenic variants in *THRA* are reported much less frequently than in *THRB*. The condition is rarely suspected due to normal levels of TSH and FT4. Symptoms of RTHα are caused by T3-resistance in tissues where TRα is the predominant receptor. The phenotype of RTHα is not univocal and patients present with a varying degree of delayed development of skeletal, motor, and neuropsychological function [35].

The 3 siblings in our study and their father presented similar features; short stature, short limbs, increased head circumference, and numerous moles. When the index patient was born, the mother immediately recognized common facial features and body compositions of the affected father and siblings. We therefore hypothesize that there may be visible signs present already at birth that may aid early identification of RTHα. Furthermore, clinical features were characterized by delayed language development, motor dyscoordination, fatigue, constipation, and obesity. Delayed language development, obesity, low height, and learning disabilities were the main reasons for early assessment in the specialist health care. All 4 patients were tested for thyroid function during childhood or adolescence. Due to normal TSH and FT4, hypothyroidism was considered less likely although the patients presented typical symptoms. Attempts to reveal a genetic etiology were performed over a timespan of 5 years until the disease-causing *THRA* etiology was disclosed by analysis of a gene panel for intellectual disability of the index patient at age 18 years. Thereafter, extensive thyroid hormone testing at admission to the outpatient thyroid clinic revealed decreased FT4/FT3 ratio (Fig. 3) and rT3 compared with healthy controls. Similar results are reported by others [12, 36].

Previously, the same variant was reported in 4 patients with hypothyroidism from 2 separate families, and functional studies showed that p.(Ala263Val) resulted in reduced T3-binding and inhibited the transcriptional activity of the wild-type receptor in a dominant negative manner [12, 36]. Furthermore, a different substitution of the same amino acid, p.(Ala263Ser), was reported in 7 patients from a family with mild symptoms of hypothyroidism [13]. Based on this, the c.788C > T, p.(Ala263Val) variant was classified as pathogenic according to ACMG-AMP guidelines [37].

This is the third reported family with the missense variant c.788C > T, p.(Ala263Val) in *THRA*. In the first family, 3 patients, a mother and 2 sons, were treated with levothyroxine from early childhood [12]. The mother had tentatively been treated as a toddler with levothyroxine which improved her growth and constipation. When 2 of her sons at age 3 years presented similar features and symptoms as their mother, they were also offered levothyroxine treatment, although blood tests could not confirm hypothyroidism. In the second family, levothyroxine treatment was started in a 17-year-old relatively asymptomatic boy in whom the mutation was diagnosed during investigation for possible delayed puberty [36].

We note that the index patient scored below 1 SD from the mean for 3 auditory tasks when evaluated as a child. Recently,

Table 3. Biochemical characteristics

	Index Patient	Patient 2	Patient 3	Patient 4	Mother[a]	Reference ranges
Hemoglobin	**11.4**	14.1	**11.6**	13.8	12.3	age ≥ 12 F: 11.7-15.3, M: 13.4-17 g/dL
EVF	**0.32**	0.42	0.36	0.42	0.38	age ≥ 12 F: 0.35-0.46, M: 0.40-0.50
MCV	88	94	94	90	98	80-100 fL
HbA1C	33	39	44	39	**58**	20-42 mmol/mol
C-peptide fasting	**1749**	898	**1690**	1105	947	300-1480 pmol/L
Total cholesterol	4.7	6.1	5.5	5.2	**3.8**	age 18-29: 2.9-6.1 age ≥ 50 3.9-7.8 mmol/L
LDL cholesterol	3.25	4.75	**4.3**	3.55	**1.63**	age 18-29: 1.5-4.2, age 50-79: 2.1-4.9 mmol/L
HDL-cholesterol	0.97	1.09	0.97	1.33	1.7	F: 1.0-2.7, M: 0.8-2.1 mmol/L
LDL/HDL	3.4	**4.4**	**4.4**	2.7	**0.96**	Recommended ratio: 1-3.5
Lipoprotein (a)	<20	<20	**114**	**131.9**	**238**	>75 nmol/L increase risk of atherosclerosis
Haptoglobin	1.8	**2.5**	**2.2**	**2.8**	1.5	0.4-2.1 g/L
Lactate dehydrogenase	181	**290**	**206**	182	121	age 18-69: 105-205 U/L
Total CK (>99% CK-MM)	**125**	**345**	173	197	79	F ≥ age 18: 35-210, M: age 18-49:50-400, M: age ≥ age 50: 40-280 U/L
CK-MB	2	4	2	2	3	≤5 µg/L
Androstenedione	3.5	2.9	6.9	**5**	**4.6**	F: 0.9-7.9, F > 50 years: 0.5-2.9, M: 1.2-4.7 nmol/L
IGF-1	25	16.4	13.1	18.5	9.2	age 19-24: 10-51, age 25-29: 9-34, age ≥ 50: 4-22 nmol/L
SHBG	36	50	28	25	124	F: 23-100, M age < 60: 8-60, age > 60: 15-90 (nmol/L)

Values outside the reference ranges are marked in bold.
Abbreviations: CK-MM/CK-MB, skeletal muscle/cardiac muscle isoenzyme of creatinine kinase; EVF, erythrocyte volume fraction; HbA1C, glycated hemoglobin A1C; IGF-1, insulin-like growth factor-1; MCV, mean corpuscular volume; SHBG, sex hormone–binding globulin.
[a]The mother served as a control. RR for the mother: SHBG (23-150 nmol/L).

THRA was implicated in the normal development of hearing in mice [38], and the authors suggested THRA patients may present with mild hearing loss.

According to the reported RTHα cases listed in the Human Gene Mutation database professional (HGMD Pro), accessed September 21, 2022, treatment with thyroxine has been tried in 21 patients with 14 different *THRA* mutations. Thyroxine treatment was started before the age of 3 years in 6 patients, 3 patients started treatment as adults, and 15 patients in childhood or adolescence [7, 8, 11, 12, 36, 39-46]. Treatment of patients with mutations in the C-terminal segment of the ligand-binding domain or in patients with nonsense or frameshift variants gave limited or no benefit [39-41]. Treatment seems to give better response when started at an early age and in patients with missense variants located in the LBD of *THRA* common for the TRα1 and TRα2 isoforms [11, 42].

Treatment with levothyroxine (LT4) in early childhood is reported to have a beneficial effect on growth and development, improvement of motor dyscoordination, constipation, and increase basal metabolism. To date, effects of LT4 have not been clearly demonstrated on heart rate, and only a limited effect has been shown on cardiac function measured by echocardiography [39, 40]. The previously untreated adult patients presented in this study have deficits caused by pathogenic variants in the LBD of *THRA* common for the TRα1 and TRα2 isoforms. Thyroxine may have less benefit in untreated adult patients with such RTH mutations and to which extent they will benefit from thyroxine treatment remains to be seen.

Both bone and the central nervous system develop most rapidly before 3 years of age, and for patients with RTHα it may be crucial to start high dosage levothyroxine treatment as infants. The effects of LT4 treatment depend on the severity and the location of the mutation. For those who have responded favorably, the treatment has increased growth and basal metabolism, ameliorated constipation, improved concentration, alertness, muscle coordination, and lipid profile and reduced weight. It is unclear whether the treatment improves cognitive function. There is limited knowledge of the effect of liothyronine (LT3) treatment in this patient group [8]. It remains to further test the effect of treatment with LT4 or LT3 in adults with RTHα. Results from patient-related outcome measures have not been published.

The assumption that treatment with LT4 from childhood in patients with RTHα may ameliorate patients' phenotype is supported by this study. The 4 previously described patients with the same *THRA* variant seem to have had milder symptoms than the 4 untreated adult patients assessed in the present study, who all presented varying degrees of constipation, tiredness, fatigue, concentration problems, social dysfunction, low mood, and obesity. More pronounced symptoms might also reflect different phenotypes in patients with the same variant in *THRA*.

Conclusion

Patients with RTHα typically present normal thyroid function tests when testing only TSH and FT4. However, typical clinical features together with symptoms of hypothyroidism and specific laboratory findings (low FT4/FT3 ratio, high FT3) should raise suspicion of RTHα and be followed by genetic testing (sequencing of the THRA gene). The importance of early diagnosis is crucial as treatment in early childhood might

improve growth and neuropsychological development. Further studies are needed to assess potential effects of levothyroxine treatment when started in adulthood.

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Author Contributions

All authors contributed to the design, collation of data and manuscript preparation.

Disclosures

The authors declare no conflicts of interest.

Data Availability

All data are presented in the article.

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