DOI: 10.4274/jcrpe.galenos.2020.2019.0190

THE CLINICAL SPECTRUM OF RESISTANCE TO THYROID HORMONE ALPHA IN CHILDREN AND ADULTS

Short title: Resistance to Thyroid Hormone Alpha

İbrahim Mert Erbaş, Korcan Demir
Division of Pediatric Endocrinology, Faculty of Medicine, Dokuz Eylül University, İzmir, Turkey

Corresponding Author:
Assoc. Prof. Dr. Korcan Demir, Division of Pediatric Endocrinology, Faculty of Medicine, Dokuz Eylül University, İzmir, Turkey
Phone: 02324126077
E-mail: korcan.demir@deu.edu.tr, korcandemir@gmail.com
15.11.2019
26.04.2020

Abstract
Resistance to thyroid hormone alpha (RTHα) occurs due to pathogenic heterozygous variants in *THRA*. The entity was described in 2012 and, until now, a small number of patients with varying severity have been reported. With this review, we summarize and interpret the heterogeneous clinical and laboratory features of all published cases, including ours. Many symptoms and findings are similar to those seen in primary hypothyroidism. However, thyroid-stimulating hormone levels are normal. Free T3 levels are in the upper half of normal range or high and free T4 levels are low or in the lower half of normal range. Alterations in free T3 and free T4 may not be remarkable particularly in adults, possibly contributing to underdiagnosis. In such patients, low reverse T3 levels, normo- or macrocytic anemia or, particularly in children, mildly elevated creatine kinase levels would warrant *THRA* sequencing. Treatment with L-thyroxine results in improvement in some clinical findings.
Key words: Constipation, developmental delay, growth failure, central hypothyroidism, autism spectrum disorder, LT4, impaired sensitivity to thyroid hormone

Introduction

Thyroid gland has important roles in regulation of energy homeostasis, skeletal growth, cardiac and gastrointestinal functions, and maturation of the central nervous system (1). Thyrotropin-releasing hormone (TRH) from hypothalamus stimulates the pituitary gland to release thyroid-stimulating hormone (TSH), which provides synthesis and secretion of thyroid hormones (TH). The term TH comprises T4 (thyroxine, prohormone, predominant product of thyroid) and T3 (triiodothyronine, the bioactive hormone). A negative-feedback mechanism provides balance between thyroid hormone levels and TRH-TSH production (2).

TH enter the cell via a number of membrane transporters, such as monocarboxylate transporter 8 (MCT8) especially in the central nervous system (3). Intracellular deiodinase enzymes regulate the TH concentrations, which convert T4 to T3 and various metabolites (4). T3 binds nuclear receptor proteins and regulates target gene transcription. In the absence of T3, receptor-protein complex represses basal gene transcription (5). There are two types of TH receptors (TR): alpha and beta. These receptors are highly homologous and encoded by *THRA* (chromosome 17) and *THRB* (chromosome 3), respectively. TRα has two isoforms produced with alternative splicing. TRα1 is mainly expressed in the central nervous system, bone, myocardium, skeletal muscle and gastrointestinal tract, while TRα2 is expressed in various tissues but has no binding site for T3 and thus its function is enigmatic (6, 7). TRβ1 is predominantly expressed in liver, kidney, thyroid gland, brain, pituitary, and inner ear. TRβ2 expression is limited to the hypothalamus, pituitary gland inner ear and retina, which plays the main role in hypothalamic-pituitary-thyroid (HPT) axis (6-8).

Variants in TR genes cause particular forms of resistance to thyroid hormone (RTH) (9). The first instance of this disease spectrum was reported by Refetoff *et al.* in 1967 (10); however, demonstration of underlying genetic defect in *THRB* took more than two decades (11). Pathogenic variants in *THRB* result in RTH beta (RTHβ, dominant OMIM #614450 and recessive OMIM #274300). The incidence of RTHβ is reported to be approximately 1/40000 and it is characterized by goiter, tachycardia, hyperactivity, failure to thrive and cognitive impairments with high serum thyroid hormone levels, but normal or mildly elevated TSH (12-14). The first case with resistance to TRα (RTHα, OMIM # 614450) due to a pathogenic heterozygous variant in *THRA*

was published in 2012 by Bochukova *et al*. (15). To date, 40 cases (13 adults, 27 children) from 28 different families with 25 different variants in *THRA* gene were published in the literature (Tables 1, 2) (15-32).
Main symptoms and findings of RTHα include varying degrees of constipation, developmental delay, growth failure, and anemia, which are associated with the tissues where TRα is the main TR and are common to primary hypothyroidism and RTHα. In the former, there is inadequate TH to induce TRα while reduced activity of TRα is the case in the latter (33). Furthermore, there are interesting additional features in some of the cases with RTHα including skin tag (18, 19, 25), epilepsy (18, 23), and individual clinical picture or laboratory findings getting less remarkable with age (17, 24). The disease is thought to be underdiagnosed given that serum TH levels are not distinctive as in RTHβ and TSH is not elevated since TRβ is intact (33, 34).

Genetics
Until today, 25 different variants in *THRA* have been published (Tables 1, 2). Six variants were inherited from an affected parent. Three of the 25 variants were frameshift, which affected four cases more severely (16, 18, 24). Three distinct variants were resulting in a premature stop codon (21, 28, 31). Most of the variants in *THRA* were missense (15, 19-26, 29, 30, 32). All of RTHα patients were heterozygous; showing that mutant TRα had a dominant-negative effect on wild-type receptor, like RTHβ (33). On the other hand, some of the variants were not functionally characterized (20, 21, 26-29, 31). In addition, one of the variants (c.1044G>T) found among subjects with autism spectrum disorder was synonymous (26).
The reported cases showed that there was a genotype-phenotype correlation in patients with RTHα. Regarding this finding, the most severe cases had frameshift variants, but missense variants usually caused a milder phenotype (18, 21, 24). And also, patients with the same variants in *THRA* can present different clinical phenotypes, suggesting that extra alterations such as cofactors figure TH activity (35).
It was described that with high T3 levels, mutant TRα can exhibit some degree of transcriptional activity like its wild-type receptor. This finding suggests that increased circulating T3 levels might have beneficial effects in reversing dominant-negative activity of mutant TRα, while it is not unclear whether high levels of T3 are a result of a compensatory mechanism (19, 23, 24).
Except one case with a mutation in both TRα1/2, who presented with severe atypical malformations (22), similar clinical features were observed due to variants affecting either TRα1 alone or TRα1/2 (33).

Pathophysiology
The mutant TRα behaves as a dominant-negative repressor of T3 target gene expression in RTHα. And also it inhibits the function of wild-type TR (15). TRα and TRβ act via transcriptional repressors like nuclear receptor corepressor-1 (NCoR1), in the lack of T3. This effect results in modification of histone deacetylase (HDAC) enzymes to a co-repressor complex, which suppresses basal T3 target gene transcription with remodeling of chromatin (36). When T3 binds to its receptors, a structural change begins, leading disruption of TR and NCoR1. Furthermore, modification of nuclear receptor coactivators starts the expression of T3 target genes (37, 38).
If TRα is mutant, it cannot be able to release NCoR1 as a response to T3. Consequently, T3 target gene transcription remains suppressed because of the inhibition of wild-type TR with constant HDAC induced chromatin remodeling. In the light of this molecular information, RTHα demonstrates clinical features with reduced T3 action in related tissues. In addition, a dominant-negative potential of the mutant TRα determines the severity of disease (38).

Clinical features
The first experimental study about TRα was reported in 1997, 15 years before the first human cases, showing that a TRα knocked-out mouse had postnatal growth arrest with delayed maturation in small intestine and bones (39).
Data regarding physical features of the patients with RTHα are generally limited and heterogeneous in the published reports. No descriptive data were given for seven children who were detected to have *THRA* variants during genetic analyses for autism spectrum disorder (20, 26). The clinical features and underlying mechanisms mainly derived from animal studies are summarized in Table 3.
Appearance
Patients with RTHα are usually born after an uneventful pregnancy (33). In severe cases, macroglossia, coarse facial features, and umbilical hernia have been noticed during the early infancy (18, 24, 32). However, there were also two children with no suggestive symptoms or clinical findings associated with hypothyroidism, who were diagnosed by family screening (24).
Coarse face including macroglossia, flattened large nose, thick lips, deep voice, hoarse cry are the common features in nearly one third of the patients with RTHα (15, 16, 18, 19, 21-25, 28-32). In addition, micrognathia and/or hypertelorism were reported in several cases (21, 22).
Rough and dry or thickened skin reflecting hypothyroidism was reported especially in children rather than adults (16, 21, 28, 31). In mice with mutant TRα, tissue iodothyronine deiodinase (DIO) 3 levels were reduced (40). In addition, topical inhibition of DIO3 enzyme was demonstrated to increase keratinocyte proliferation in animal models (40, 41). Therefore, symptoms about

skin in TRα patients thought to be related with these changes. Skin tags were present in 21% of cases with RTHα (Seven among 33 cases with available data) (18, 19, 24, 25). Bilateral inguinal hernia and umbilical hernia were defined in two children (25, 29).

Skeletal findings

Skeletal manifestations such as growth retardation, patent cranial sutures, epiphyseal dysgenesis, and delayed dental eruption have been demonstrated in mice with mutant TRα1 receptor (42, 43). In addition, mice with *THRA* variant presented decreased endochondral and intramembranous ossification with retarded closure of skull sutures (44). Delayed ossification in these animal models caused impaired bone remodeling and thus short stature with skeletal deformities. However, bone strength was normal, which can explain why pathologic fractures are not seen in humans with RTHα (43). Further molecular studies displayed that mutant TRα caused reduced transcription of target genes such as growth hormone receptor, insulin-like growth factor-1 (IGF-1) or its receptor and fibroblast growth factor receptor-1 or 3. Moreover, decreased signaling in post-receptor pathways in osteoblasts or chondrocytes was reported (45-50).

Short stature is one of the most common clinical findings in children with RTHα (12 among 20 children with available data, 60%). Ten of the 12 short children were not treated with L-thyroxine (LT4) before diagnosis and the lowest height SD score was -3.1 (15, 16, 21, 23-25, 28, 29). A previously untreated three years and 11 months old Chinese female was reported with a height of 85.5 cm, SD score was not provided (31). All of the remaining eight children with normal height had missense variants. Six of them (85.7%) had a height SD score between -1.66 and 0; none of them had received any treatment. Half of the 12 adult cases with available data had normal height (maximum, 186 cm); all of them had missense variants and three had received LT4 starting from childhood (16, 18, 19, 21-24).

Wormian bones in skull sutures were present in 10 among 31 cases with available data (32%) (15, 24, 25). Various skeletal deformities including delayed bone age, genu valgum, coxa valga, short tubular hand bones, late closure of the fontanelles, femoral epiphyseal dysgenesis were also reported (15, 19, 21, 22, 24, 25, 28, 29, 31). Mesomelic shortening of upper and lower limbs cause increased sitting/total height ratio (21, 24, 25). Skull radiography showed cranial hyperostosis in some patients (18, 19, 24). Espiard *et al.* (22) reported a 27 years-old case with RTHα, who had severe deformities like cleidocranial dysplasia (clavicular agenesis, humero-radial synostosis, syndactyly of toes, agenesis of the 12th ribs and scoliosis). However, these several findings were atypical for RTHα and were not reported in any other case. Bone mineral density was reported normal in three adult patients (19).

Normally, tooth eruption is expected to occur before 13 months of age (51). Delayed tooth eruption was detected in eight among 18 children with available data (44%) (15, 24, 25, 29).

Bochukova *et al.* reported a mild hypermobility and ligamentous laxity in ankle and knee (15). Although muscle tone was decreased in some cases with RTHα, their muscle strength was almost normal (15).

Neuromotor development

T3 and its receptors play a major role in neuronal migration, synaptogenesis, maturation, myelination and differentiation of oligodendrocytes or glial cells (52). That is why TRα knockout animals showed a severe delay in postnatal development and locomotor dysfunction (53). It is defined that TRα had significant effects on cerebellar formation and hippocampal functions and TRα mutant mouse models had reduced brain mass (54-56). Wilcoxon *et al.* defined behavioral inhibition, decreased functions in learning and memory in mice lacking all isoforms of TRα (57).

In infants with RTHα, delayed milestones for motor and speech abilities are the most common symptoms [noted in 34 among 40 cases (85%)] (15, 16, 18-21, 23-26, 28-32). Reduced IQ, notable impairments in cognitive functions, slow motion movements, evident motor incoordination as dyspraxia, ataxia, broad or unstable gait are some of the clinical findings in neurological examination (15, 18, 19, 24, 28, 32). Remarkably, two cases with the A263V variant were able to attend university without LT4 treatment (Demir-unpublished observation of Patient 3.III.1 in reference 24, 25). First patient had no symptoms and was detected during family screening (24). The second case had mild delay in motor and mental development during childhood and received little teaching support (25). Axial hypotonia, slow motor development can also be seen (23). Clumsiness due to motor incoordination and difficulty with fine motor abilities reported in some patients, who were incapable of writing or drawing (15, 18, 28). Speech delay and dysarthric or slow speech are significant symptoms that are seen in the majority of cases (15, 16, 18, 19, 21, 23, 24, 28). Macrocephalia, represented as a common clinical finding (23 among 33 cases with available data, 70%) (15, 16, 18-25, 29-31).

Furthermore, Demir *et al.* (24) reported a 35-year-old adult case, whose developmental delay during childhood was more remarkable compared to her affected son. On the other hand, she had an attenuated clinical picture (mild intellectual deficit, no cardiac problems, and normal thyroid function tests) at the age of presentation, despite being not treated. Similar observations were also made in a mouse model with a heterozygous TRα1 variant at the same position (53, 58). These mice showed severe but transient impairment of postnatal development and growth. The mechanisms underlying the amelioration of deficits caused by these TRα1 variants with age are unknown.

Seizures after stimulation with light or audio and abnormal evolution of GABAergic neurons in TRα1 mutant mice correlated with epilepsy in human cases (42, 59, 60). To date, three cases with RTHα were reported to be suffering from epileptic seizures in childhood (18, 23, 32).

A notable anxiety in unfamiliar environments and reduced cognitive functions were observed in TRα1 mutant animal models (59). Another study demonstrated that TRα1 mutant mice developed depressive and anxious behaviours (60). Kalikiri *et al.* (26) investigated 30 children diagnosed as autism spectrum disorder and found *THRA* variants in six of them. Unfortunately, no additional data of these children were provided. Coexistence of autism spectrum disorder and RTHα was reported in two more patients, suggesting that it should be a common clinical presentation (20, 31).

Constipation

TRα is the dominant TR in intestinal tract (6, 7). In a study with TRα1 mutant mice models, shortened villi, increased differentiation in crypt cells and decreased stem cell proliferation were observed (62). Independent of age, constipation is a leading clinical symptom being reported in 26 among 31 cases with available data (84%) (15, 16, 18, 19, 21, 23-25, 28, 29, 31, 32). The atypical patient reported by Espiard *et al.* (22), was the only patient developing chronic diarrhea at the age of 12. Abdominal radiographs showed dilated bowels. Decreased peristalsis was also observed by colonic manometry in several cases with RTHα (15, 18).

Cardiovascular system

TRα1 is expressed in myocardium and it was suggested to be responsible for cardiac myoblast differentiation in experimental studies (63). Mutant TRα1 mice models showed hypothyroidism symptoms in the cardiovascular system, such as bradycardia or weak cardiac contractions (64). Makino *et al.* (65) found that predominant TR in mouse coronary smooth muscle cells was TRα, and suggested that coronary vascular tone was regulated by TRα. However, cardiac pathologies or symptoms do not seem to be common in humans with RTHα. Although most of the patients had normal heart rate or blood pressure, some cases were reported to have bradycardia (15, 18, 19). Until today, three cases with cardiomyopathy and one case with pericardial effusion have been reported (21, 24).

Metabolic problems and fertility

TRα null or mutant mice had lower core body temperature due to impaired facultative thermogenesis (66). Although most of the animal models with mutant TRα were thin, several studies described obesity (58). Also in the same study, it was reported that the TRα1R384C mutant mice were hyperphagic but resistant to obesity (58). It was suggested that, centrally leaded hypermetabolism through apo-TRα1 resulted in lower adipose tissue and lesser body weight (67). However, in humans diagnosed as RTHα, eight among 33 cases with available data (24%) were obese; six of them were adults (15, 18, 23, 24). Low resting energy expenditure (metabolic rate) was also reported in some patients with RTHα (15, 18, 19, 22). In addition to these, total cholesterol and low-density lipoprotein (LDL) levels were high in several patients (16, 18, 19).

As RTHα can be seen in children of affected adults, it supports that fertility might be unaffected in either gender. Regular pregnancies after spontaneous conception were reported in even moderately affected and untreated female RTHα cases (24). Only one patient had late-onset of puberty and menarche at 16 years-old, with normal gonadotropin and estrogen levels (18).

Laboratory

Unfortunately, various relevant measurements were lacking in some of the reported cases. In addition, while the majority of data in the literature were presented as exact values with their reference ranges, some reports included only categorized data (Tables 1, 2).

Thyroid function tests

Thyroid function tests of individuals suspected to have RTHα should be cautiously interpreted since the literature data were derived from cases with varying severity of RTHα from different age groups. Abnormal TH levels are more likely to be found in severe cases and in children. Since the TH and TSH levels seem to differ with previous LT4 use, we chose to evaluate the data belonging to the cases who had not received LT4 previously (LT4-naive) separately from the patients who were analyzed after discontinuation of LT4 treatment.

Individuals who had not receive any thyroid hormone

A normal neonatal congenital hypothyroidism screening result [T4 62 nmol/L (-1.3 SD), TSH 1 mIU/L] was reported in a case with RTHα, who also had an uneventful neonatal period (23). TSH levels were all normal in affected children. Among the adult patients, an atypical case with severe malformations was the only one with abnormal TSH (0.343 mIU/L, normal range 0.4-3.6) (22) (Figure 1).

Differences of TH levels among treatment-naive children and adults are also shown in Figure 1. All of the free T3 and majority of total T3 levels were in the upper half of normal range or high. Elevated free T3 (fT3) levels were found only in treatment-naive children but not in such adult cases. All of the free T4 and majority of total T4 levels were low or in the lower half of normal range. Low fT4 concentrations were more frequently present among children. In adult patients, free T4 (fT4) levels were all normal except for one (30).

Both fT4 and TSH were normal in 61% (11 among 18) of children and 78% (7 among 9) of adults. Normal fT3, fT4 and TSH were noted in 33% (5 among 15) and 83% (5 among 6) of children and adults, respectively (Figure 2). In such cases, a high T3/T4 ratio or low or low-normal reverse T3 (rT3) levels resulting in an increased T3/rT3 ratio can be suggestive for RTHα (33). These abnormalities in RTHα patients can be resulted by the changes of DIO1 and DIO3 levels in tissues, whose expressions are regulated by TRα. In a study, TRα1 mutant mice had raised hepatic DIO1 levels, which converts T4 to T3 (42). Therefore, this finding was related to high T3 levels and increased T3/T4 ratio in RTHα. Also decreased DIO3 levels in tissues may result in low rT3 levels, causing reduced inner-ring deiodination of T4 to rT3 (40).

Individuals who discontinued treatment

After cessation of LT4 treatment, mildly elevated TSH can be seen as was reported in one adult and one child with RTHα (17, 18). The child in whom TSH rose at the age of 11 after discontinuation of LT4 had normal pretreatment TSH levels at 5 and 6 years of age (17). On the other hand, TSH remained in normal range in three adult patients and an adolescent case (19, 25). Off thyroxine treatment, patients had marginally low or low-normal fT4. A wide range of free or total T3 data (varying from the lower half of the normal range to elevated levels) was reported. Nevertheless, rT3 levels were all low (17-19, 25).

Individuals receiving thyroid hormone

Under LT4 treatment, fT3 and fT4 levels increased in patients with RTHα, while TSH was suppressed like during treatment of central hypothyroidism (15, 17-19, 23, 24, 29). One patient with atypical phenotype was treated with liothyronine, which caused a rise in fT3 level, suppressed TSH level, and markedly reduced fT4 concentration (22).

Anemia

The relationship between anemia and hypothyroidism is well-known (68). Animal models lacking TRα demonstrated compromised erythropoiesis (69, 70). van Gucht *et al.* (71) studied progenitor cells derived from RTHα patients and showed that these cells differentiated more slowly than controls. In humans, 23 among 30 cases with available data (77%) had anemia, and it has been one of the most common findings in humans with RTHα (16, 18, 19, 21-25, 28, 29, 31, 32). The rate of anemia was similar between treatment-naive children (80%) and adults (86%) (Figure 2). In the reports where exact values were included, hemoglobin levels ranged between 8.6-10.9 g/dL and 9.6-12.9 g/dL in children and adults, respectively. In the majority, anemia was normocytic and normochromic; macrocytic anemia was described in three cases (13%) (15, 18, 22).

An increase in serum levels of IL-8, a pro-inflammatory cytokine were shown in RTHα patients. However, neutrophil or macrophage functions were found to be normal in those cases (72).

Other biochemical findings

Either thyroglobulin or urinary iodine levels are expected to be in normal range (34). Similar to primary hypothyroidism, high total cholesterol and LDL levels, low or low-normal levels of IGF-1 can be found in RTHα (33, 34).

In primary hypothyroidism, creatine kinase (CK) can be elevated as well (73). Human data demonstrate that CK might be a promising biomarker for diagnosis of RTHα particularly in children. Eight among 11 treatment-naive children (73%) with available data had elevated CK levels (range; 218-981 U/L, 1.3-4.36 times upper limit of normal), while all of the treatment-naive adults with available data (n=5) had normal CK levels (Figures 2 and 3) (15, 16, 22-25, 28, 29, 31). On the other hand, elevated CK levels were noted in the two children [196-213 U/L (1.03-1.31 times upper limit of normal] and three of four adult patients [364-387 U/L (1.90-2.02 times upper limit of normal], who were assessed after discontinuation of LT4 (17-19, 25).

Recently, Boumaza *et al.* reported that biofluids (urine and plasma samples) of TRα-mutant mice showed distinct metabolomic profiles from controls, including parameters such as isovalerylglycine, dimethylamine, trimethylamine, choline and hippurate. They claimed that easily accessible Nuclear Magnetic Resonance-based metabolic fingerprints of biofluids could be used to diagnose RTHα in humans (74).

Differential Diagnosis

RTHα should come to mind when various clinical features indicate hypothyroidism but TSH is normal and free T4 is low or in lower half of normal range in cases who had not received LT4 treatment (Figure 4). Parental medical history should be investigated thoroughly for similar clues due to autosomal dominant inheritance.

More common conditions including non-thyroidal illness, recovery from thyrotoxicosis, or technical assay problems may result in similar biochemical features (75). However, they are not associated with clinical features of RTHα.

Central hypothyroidism should be ruled out when free T4 low and TSH is low, normal, or slightly elevated. Presence of hypothalamic-pituitary disease, hypo- or hypersecretion of other pituitary hormones or genetic findings would indicate an etiology for central hypothyroidism (75). On the other hand, if T3 levels are elevated or close to the upper limit, the probability of central hypothyroidism is low.

Laboratory findings as elevated/normal T3, reduced rT3, normal or low T4 levels, and normal/elevated TSH are also found in MCT8 deficiency (Allan Herndon Dudley syndrome). However, clinical and laboratory signs of peripheral thyrotoxicosis are present in this disease in addition to cerebral hypothyroidism (76-79). Furthermore, MCT8 deficiency is inherited in an X-linked manner (80). That's why the mothers of affected patients are asymptomatic carriers; however, an affected parent can be found in case of RTHα (16, 21, 23-25, 77, 78).

Additional clues for RTHα in LT4-naive children and adults are free or total T3 in the upper half of normal range or above upper limit along with one of normo- or macrocytic anemia *or* mildly elevated CK *or* low rT3. Among the subjects with available data, the algorithm in Figure 4 is valid for 15 of 16 the children (94%) and for six of eight adults (75%) (15-17, 21, 22-25, 27-32). When the data of four additional adult cases, whose assessments were available after discontinuation of LT4, are included as well, the algorithm should be modified regarding T3 and TSH data given that free T3 levels may also be in the lower half of the normal range and TSH levels can be mildly elevated. In these subjects, after exclusion of central hypothyroidism, presence of either normo- or macrocytic anemia *or* mildly elevated CK values *or* low rT3 levels would be an additional clue leading to *THRA* sequencing. This approach is valid for 10 of 12 adult patients with available data (83%) (16-19, 22-24, 30). Both approaches need also be tested for their specificity in future studies.

Treatment and Outcomes

There is only limited data about the treatment RTHα, therefore long-term follow-up data is required. LT4 treatment has been the first choice until today, in order to overcome the resistance in TRα with higher dosage. T4 and rT3 levels come to the normal range by this treatment and T3 level remains high. Since feedback mechanism in HPT axis is intact, LT4 treatment causes TSH suppression in RTHα patients (15, 17-19, 23, 24, 29).

In animal models with mutant TRα, increasing serum thyroid hormone levels alleviated locomotor and behavioral irregularities (59). Therefore, LT4 supplementation to raise circulating thyroid hormone levels was suggested to be beneficial in RTHα. Bassett *et al.* (43) reported that prolonged T4 treatment advanced bone rigidity and strength in TRα mutant mice. However, it did not exert any effect on skeletal development, linear growth or mineralization of bones (43). Vennström *et al.* (58) claimed that, high doses of T3 given in the appropriate developmental time period, should improve the abnormalities depending on the mutant TRα. And they showed that metabolic symptoms of mice with mutant TRα, were well treated by T3. Regarding this, Espiard *et al.* (22) reported that their case with atypical phenotype received liothyronine treatment and presented a notable cardiac and metabolic response. Nevertheless, other parameters did not change significantly, suggesting that the variant in the case only provides limited resistance to T3.

Van Mullem *et al.* (17) reported the results of two RTHα patients (a daughter and her father, with the same variant), who were treated with LT4 for over 5 years. They showed that some clinical features such as constipation or nerve conductance were improved. However, fine motor abilities or cognitive functions did not benefit from treatment (17). On the other hand, most of the LT4 treated patients had better motor coordination, alertness, school performance, concentration or motivation (19, 25, 29, 31). They had limited benefit on linear growth (15, 17, 23). Hypotonia was ameliorated and accelerated neuromotor development was observed in children as well (23, 31, 32). Thus, if the treatment was started at an early age, the benefits on development and growth would be more distinguishable. As described in van Mullem's report (17), constipation improved with LT4 treatment in most of the other RTHα cases (15, 19, 25, 29).

With the peripheral effects of LT4 treatment, increases in SHBG or IGF-1 levels can be seen as previously reported in RTHα patients. In addition to this, CK or cholesterol levels were reduced in these cases, reflecting the improved tissue response to TH (15, 17-19, 23-25). Also it was defined that when LT4 treatment was interrupted, all these indicators turned back to pretreatment levels (17). Korkmaz *et al.* (29) reported a decrease in SHBG levels and found IGF-1 levels unaltered after LT4 treatment in a patient with RTHα, although the TSH level was suppressed and CK levels were decreased. Moran *et al.* (18) reported a progressive rise in bone turnover markers after LT4 treatment in a case with RTHα. Growth hormone was added to LT4 therapy due to low-normal IGF-1 levels in an affected child, but sufficient improvement in linear growth could not be observed (17).

Anemia seems to be unresponsive to LT4 treatment, as described in most of the RTHα cases (18, 19, 25, 29). Although van Gucht *et al.* (71) showed that human erythroid progenitors responded to T3 exposure in an experimental study, they claimed that mutant TRα takes role in the earlier stages of erythropoiesis, which they could not examine in their research. In addition, LT4 treatment had a limited effect on cardiac functions in several cases with RTHα (18, 19). Increase in heart rate was observed in one patient after LT4 treatment (22).

Patients who had frameshift variants in *THRA,* including the carboxy-terminal part of TRα1, had varying responses to LT4 treatment. Like their severity of clinical presentation, this situation was also associated with the definite location of variant or how degree this section was affected (18, 24, 17). Also, their skeletal abnormalities did not respond to LT4 treatment (17, 18, 24).

Since LT4 administration to RTHα patients will stimulate TRβ in TRβ-dominant tissues more than needed, development of TRα1-selective thyromimetics would be ideal (33, 81). Alternative investigations targeted the HDAC activity or interaction with corepressor complex to inhibit the dominant-negative effect of wild-type analogue of mutant TRα1. It was shown in a mice study that a mutation in NCoR can disrupt its coaction with TRα1 and reverses the effects of mutant TRα (82). A HDAC inhibitor, suberoylanilide hydroxamic acid (SAHA), was used to relieve the repression in target genes and phenotypic features were improved in TRα1 mutant mice (81, 83, 84). However, Freudenthal *et al.* showed that SAHA was unlikely to treat skeletal abnormalities and had no effect on bone structure or strength in TRα mutant mouse models (38). They claimed that alternative co-repressors beside NCoR should interact with TRα in skeletal cells (36, 38).

Conclusion

The diagnosis of RTHα is not straightforward since thyroid hormone levels might not be helpful and the entity is not widely known. Since literature data is limited about RTHα, absence of phenotypic features or laboratory findings would not exclude RTHα. Currently, only fT4 and TSH levels are recommended for evaluation of growth failure in children (85). However, these tests can be normal in a subject with RTHα and astute clinicians should do further investigations in such a case when clinical picture is similar to hypothyroidism. In addition, RTHα should be kept in mind in patients diagnosed with apparent central hypothyroidism, particularly when the exact etiology could not be detected.

References

1. Visser TJ. Regulation of thyroid function, synthesis and function of thyroid hormones. In: Vitti P, Hegedus L (Eds), Thyroid Diseases. Endocrinology. Springer, Cham, 2018; p 1-30.
2. Fekete C, Lechan RM. Central regulation of hypothalamic-pituitary-thyroid axis under physiological and pathophysiological conditions. Endocr Rev 2014; 35(2):159-94.
3. Visser WE, Friesema EC, Visser TJ. Minireview: thyroid hormone transporters: the knowns and the unknowns. Mol Endocrinol 2011; 25:1-14.
4. St Germain DL, Galton VA, Hernandez A. Minireview: defining the roles of the iodothyronine deiodinases: current concepts and challenges. Endocrinol 2009; 150:1097-107.
5. Horlein AJ, Heinzel T, Rosenfeld MG. Gene regulation by thyroid hormone receptors. Curr Opin Endocrinol Diabetes 1996; 3:412-6.
6. Lazar MA. Thyroid hormone receptors: multiple forms, multiple possibilities. Endocr Rev 1993; 14:184-93.
7. Cheng SY, Leonard JL, Davis PJ. Molecular aspects of thyroid hormone actions. Endocr Rev 2010; 31:139-70.
8. Ng L, Cordas E, Wu X, Vella KR, Hollenberg AN, Forrest D. Age-Related Hearing Loss and Degeneration of Cochlear Hair Cells in Mice Lacking Thyroid Hormone Receptor β1. Endocrinology 2015; 156(10):3853-65.
9. Refetoff S, Bassett JH, Beck-Peccoz P, Bernal J, Brent G, Chatterjee K, De Groot LJ, Dumitrescu AM, Jameson JL, Kopp PA, Murata Y, Persani L, Samarut J, Weiss RE, Williams GR, Yen PM. Classification and proposed nomenclature for inherited defects of thyroid hormone action, cell transport, and metabolism. Thyroid 2014; 24(3):407-9.
10. Refetoff S, DeWind LT, DeGroot LJ. Familial syndrome combining deaf-mutism, stippled epiphyses, goiter, and abnormally high PBI: possible target organ refractoriness to thyroid hormone. J Clin Endocrinol Metab 1967; 27:279-94.
11. Sakurai A, Takeda K, Ain K, Ceccarelli P, Nakai A, Seino S, Bell GI, Refetoff S, DeGroot LJ: Generalized resistance to thyroid hormone associated with a mutation in the ligand-binding domain of the human thyroid hormone receptor β. Proc Natl Acad Sci USA 1989; 86:8977-81.
12. Lafranchi SH, Snyder DB, Sesser DE, Skeels MR, Singh N, Brent GA, Nelson JC. Follow-up of newborns with elevated screening T4 concentrations. J Pediatr 2003; 143(3):296-301.
13. Jackowski T, Petriczko E, Horodnicka-Józwa A, Walczak M. Thyroid hormone resistance syndrome - own experiences. Pediatr Endocrinol Diabetes Metab 2017; 23(4):209-14.
14. Pappa T, Refetoff S. Human Genetics of Thyroid Hormone Receptor Beta: Resistance to Thyroid Hormone Beta (RTHβ). Methods Mol Biol 2018; 1801:225-40.
15. Bochukova E, Schoenmakers N, Agostini M, Schoenmakers E, Rajanayagam O, Keogh JM, Henning E, Reinemund J, Gevers E, Sarri M, Downes K, Offiah A, Albanese A, Halsall D, Schwabe JW, Bain M, Lindley K, Muntoni F, Vargha-Khadem F, Dattani M, Farooqi IS, Gurnell M, Chatterjee K: A mutation in the thyroid hormone receptor alpha gene. N Engl J Med 2012; 366(3):243-9.
16. van Mullem A, van Heerebeek R, Chrysis D, Visser E, Medici M, Andrikoula M, Tsatsoulis A, Peeters R, Visser TJ. Clinical phenotype and mutant TR α1. N Engl J Med 2012; 366(15):1451-3.
17. van Mullem AA, Chrysis D, Eythimiadou A, Chroni E, Tsatsoulis A, de Rijke YB, Visser WE, Visser TJ, Peeters RP. Clinical phenotype of a new type of thyroid hormone resistance caused by a mutation of the TRα1 receptor: consequences of LT4 treatment. J Clin Endocrinol Metab 2013; 98(7):3029-38.
18. Moran C, Schoenmakers N, Agostini M, Schoenmakers E, Offiah A, Kydd A, Kahaly G, Mohr-Kahaly S, Rajanayagam O, Lyons G, Wareham N, Halsall D, Dattani M, Hughes S, Gurnell M, Park SM, Chatterjee K. An adult female with resistance to thyroid hormone mediated by defective thyroid hormone receptor α. J Clin Endocrinol Metab 2013; 98(11):4254-61.
19. Moran C, Agostini M, Visser WE, Schoenmakers E, Schoenmakers N, Offiah AC, Poole K, Rajanayagam O, Lyons G, Halsall D, Gurnell M, Chrysis D, Efthymiadou A, Buchanan C, Aylwin S, Chatterjee KK. Resistance to thyroid hormone caused by a mutation in thyroid hormone receptor (TR) α1 and TRα2: clinical, biochemical, and genetic analyses of three related patients. Lancet Diabetes Endocrinol 2014; 2(8):619-26.
20. Yuen RK, Thiruvahindrapuram B, Merico D, Walker S, Tammimies K, Hoang N, Chrysler C, Nalpathamkalam T, Pellecchia G, Liu Y, Gazzellone MJ, D'Abate L, Deneault E, Howe JL, Liu RS, Thompson A, Zarrei M, Uddin M, Marshall CR, Ring RH, Zwaigenbaum L, Ray PN, Weksberg R, Carter MT, Fernandez BA, Roberts W, Szatmari P, Scherer SW. Whole-genome sequencing of quartet families with autism spectrum disorder. Nat Med 2015; 21(2):185-91.
21. Tylki-Szymanska A, Acuna-Hidalgo R, Krajewska-Walasek M, Lecka-Ambroziak A, Steehouwer M, Gilissen C, Brunner HG, Jurecka A, Rozdzynska-Swiatkowska A, Hoischen A, Chrzanowska KH. Thyroid hormone resistance syndrome due to mutations in the thyroid hormone receptor α gene (THRA). J Med Genet 2015; 52(5):312-6.
22. Espiard S, Savagner F, Flamant F, Vlaeminck-Guillem V, Guyot R, Munier M, d'Herbomez M, Bourguet W, Pinto G, Rose C, Rodien P, Wemeau JL. A novel mutation in THRA gene associated with an atypical phenotype of resistance to thyroid hormone. J Clin Endocrinol Metab 2015; 100(8): 2841-48.
23. van Gucht AL, Meima ME, Zwaveling-Soonawala N, Visser WE, Fliers E, Wennink JM, Henny C, Visser TJ, Peeters RP, van Trotsenburg AS. Resistance to thyroid hormone alpha in an 18-month-old girl: clinical, therapeutic, and molecular characteristics. Thyroid 2016; 26(3):338-46.

24. Demir K, van Gucht AL, Büyükinan M, Çatlı G, Ayhan Y, Bas¸ VN, Dündar B, Özkan B, Meima ME, Visser WE, Peeters RP, Visser TJ. Diverse genotypes and phenotypes of three novel thyroid hormone receptor-α mutations. J Clin Endocrinol Metab 2016; 101(8):2945-54.
25. Moran C, Agostini M, McGowan A, Schoenmakers E, Fairall L, Lyons G, Rajanayagam O, Watson L, Offiah A, Barton J, Price S, Schwabe J, Chatterjee K. Contrasting phenotypes in resistance to thyroid hormone alpha correlate with divergent properties of thyroid hormone receptor α1 mutant proteins. Thyroid 2017; 27(7):973-82.
26. Kalikiri MK, Mamidala MP, Rao AN, Rajesh V. Analysis and functional characterization of sequence variations in ligand binding domain of thyroid hormone receptors in autism spectrum disorder (ASD) patients. Autism Res 2017; 10(12):1919-28.
27. Sun H, Chen XL, Chen T, Wu HY, Xie RR, Wang FY, Wang XY, Chen LQ. [Clinical characteristics of thyroid hormone resistance syndrome in two cases with different subtypes]. Zhonghua Er Ke Za Zhi 2017; 55(12):953-6.
28. Sun H, Wu H, Xie R, Wang F, Chen T, Chen X, Wang X, Flamant F, Chen L. New Case of Thyroid Hormone Resistance α Caused by a Mutation of THRA /TRα1. J Endocr Soc 2019; 3(3):665-9.
29. Korkmaz O, Ozen S, Ozdemir TR, Goksen D, Darcan S. A novel thyroid hormone receptor alpha gene mutation, clinic characteristics, and follow-up findings in a patient with thyroid hormone resistance. Hormones (Athens) 2019; 18(2):223-7.
30. Wejaphikul K, Groeneweg S, Hilhorst-Hofstee Y, Chatterjee VK, Peeters RP, Meima ME, Visser WE. Insight Into Molecular Determinants of T3 vs T4 Recognition From Mutations in Thyroid Hormone Receptor α and β. J Clin Endocrinol Metab 2019; 104(8):3491-3500.
31. Wang TQ, Li CP, Zhou H, Lu T, Long SS, Ma Y, Wang Y. THRA gene mutation in a child with congenital hypothyroidism. Zhonghua Er Ke Za Zhi 2019; 57(4):291-2.
32. Le Maire A, Bouhours-Nouet N, Soamalala J, Delphine MP, Paloni M, Guee L, Heron D, Mignot C, Illouz F, Joubert F, Briet C, Rodien P, Bourguet W, Flamant F, Guyot R. Two novel cases of resistance to thyroid hormone due to THRA mutation (RTHα). Thyroid 2020 DOI: 10.1089/thy.2019.0602.
33. van Gucht ALM, Moran C, Meima ME, Visser WE, Chatterjee K, Visser TJ, Pe/eters RP. Resistance to Thyroid Hormone due to Heterozygous Mutations in Thyroid Hormone Receptor Alpha. Curr Top Dev Biol 2017; 125:337-55.
34. Moran C, Chatterjee K. Resistance to thyroid hormone α-emerging definition of a disorder of thyroid hormone action. J Clin Endocrinol Metab 2016; 101(7):2636–9.
35. Refetoff S, Dumitrescu AM. Syndromes of reduced sensitivity to thyroid hormone: Genetic defects in hormone receptors, cell transporters and deiodination. Best Pract Res Clin Endocrinol Metab 2007; 21(2):277-305.
36. Astapova I, Hollenberg AN. The in vivo role of nuclear receptor corepressors in thyroid hormone action. Biochim Biophys Acta 2013; 1830:3876-81.
37. Vella KR, Ramadoss P, Costa ESRH, Astapova I, Ye FD, Holtz KA, Harris JC, Hollenberg AN. Thyroid hormone signaling in vivo requires a balance between coactivators and corepressors. Mol Cell Biol 2014; 34:1564-75.
38. Freudenthal B, Shetty S, Butterfield NC, Logan JG, Han CR, Zhu X, Astapova I, Hollenberg AN, Cheng SY, Bassett JHD, Williams GR. Genetic and Pharmacological Targeting of Transcriptional Repression in Resistance to Thyroid Hormone Alpha. Thyroid 2019; 29(5):726-34.
39. Fraichard A, Chassande O, Plateroti M, Roux JP, Trouillas J, Dehay C, Legrand C, Gauthier K, Kedinger M, Malaval L, Rousset B, Samarut J. The T3Rα gene encoding a thyroid hormone receptor is essential for post-natal development and thyroid hormone production. The EMBO Journal 1997; 16(14):4412-20.
40. Barca-Mayo O, Liao X, Alonso M, Di Cosmo C, Hernandez A, Refetoff S, Weiss RE. Thyroid hormone receptor α and regulation of type 3 deiodinase. Mol Endocrinol 2011; 25: 575-83.
41. Huang M, Rodgers K, O'Mara R, Mehta M, Abuzahra HS, Tannenbaum AD, Persons K, Holick MF, Safer JD. The thyroid hormone degrading type 3 deiodinase is the primary deiodinase active in murine epidermis. Thyroid 2011; 21: 1263-8.
42. Quignodon L, Vincent S, Winter H, Samarut J, Flamant F. A point mutation in the activation function 2 domain of thyroid hormone receptor α1 expressed after CRE-mediated recombination partially recapitulates hypothyroidism. Mol Endocrinol 2007; 21:2350-60.
43. Bassett JH, Boyde A, Zikmund T, Evans H, Croucher PI, Zhu X, Park JW, Cheng SY, Williams GR. Thyroid hormone receptor alpha mutation causes a severe and thyroxine resistant skeletal dysplasia in female mice. Endocrinol 2014; 155:3699-712.
44. Kaneshige M, Suzuki H, Kaneshige K, Cheng J, Wimbrow H, Barlow C, Willingham MC, Cheng S. A targeted dominant negative mutation of the thyroid hormone alpha 1 receptor causes increased mortality, infertility, and dwarfism in mice. Proc Natl Acad Sci USA 2001; 98:15095-100.
45. Bassett JH, O'Shea PJ, Sriskantharajah S, Rabier B, Boyde A, Howell PG, Weiss RE, Roux JP, Malaval L, Clement-Lacroix P, Samarut J, Chassande O, Williams GR. Thyroid hormone excess rather than thyrotropin deficiency induces osteoporosis in hyperthyroidism. Mol Endocrinol 2007; 21(5):1095-1107.
46. Stevens DA, Harvey CB, Scott AJ, O'Shea PJ, Barnard JC, Williams AJ, Brady G, Samarut J, Chassande O, Williams GR. Thyroid hormone activates fibroblast growth factor receptor-1 in bone. Mol Endocrinol 2003; 17(9):1751-66.

47. O'Shea PJ, Bassett JH, Cheng SY, Williams GR. Characterization of skeletal phenotypes of TRα1 and TRα mutant mice: implications for tissue thyroid status and T3 target gene expression. Nucl Recept Signal 2006; 4:e011.
48. Bassett JH, Nordström K, Boyde A, Howell PG, Kelly S, Vennström B, Williams GR. Thyroid status during skeletal development determines adult bone structure and mineralization. Mol Endocrinol 2007; 21(8):1893–1904.
49. Barnard JC, Williams AJ, Rabier B, Chassande O, Samarut J, Cheng SY, Bassett JH, Williams GR. Thyroid hormones regulate fibroblast growth factor receptor signaling during chondrogenesis. Endocrinology 2005; 146(12):5568-80.
50. Xing W, Govoni KE, Donahue LR, Kesavan C, Wergedal J, Long C, Bassett JH, Gogakos A, Wojcicka A, Williams GR, Mohan S. Genetic evidence that thyroid hormone is indispensable for prepubertal insulin-like growth factor-I expression and bone acquisition in mice. J Bone Miner Res 2012; 27(5):1067-79.
51. Keane VA. Assessment of growth. In: Kliegman RM, Stanton BF, St Geme JW III, Schor NF, eds. Nelson Textbook of Pediatrics 20th ed. Philadelphia, PA: Elsevier; 2016: chap 15.
52. Bernal, J. Thyroid hormone receptors in brain development and function. Nature Clinical Practice. Endocrinology and Metabolism 2007; 3:249-59.
53. Tinnikov A, Nordström K, Thorén P, Kindblom JM, Malin S, Rozell B, Adams M, Rajanayagam O, Pettersson S, Ohlsson C, Chatterjee K, Vennström B. Retardation of post-natal development caused by a negatively acting thyroid hormone receptor alpha1. EMBO J 2002; 21(19):5079-87.
54. Itoh Y, Esaki T, Kaneshige M, Suzuki H, Cook M, Sokoloff L, Nunez J. Brain glucose utilization in mice with a targeted mutation in the thyroid hormone alpha or beta receptor gene. Proc Natl Acad Sci USA 2001; 98(17): 9913-8.
55. Bernal J, Guadaño-Ferraz A. Analysis of thyroid hormone-dependent genes in the brain by in situ hybridization. Methods Mol Biol 2002; 202:71-90.
56. Morte B, Manzano J, Scanlan T, Vennström B, Bernal J. Deletion of the thyroid hormone receptor alpha 1 prevents the structural alterations of the cerebellum induced by hypothyroidism. Proc Natl Acad Sci USA 2002; 99(6):3985-9.
57. Wilcoxon JS, Nadolski GJ, Samarut J, Chassande O, Redei E. Behavioral Inhibition and Impaired Spatial Learning and Memory in Hypothyroid Mice Lacking Thyroid Hormone Receptor α. Behav Brain Res 2007; 177(1):109-116.
58. Vennström B, Mittag J, Wallis K. Severe psychomotor and metabolic damages caused by a mutant thyroid hormone receptor alpha 1 in mice: can patients with a similar mutation be found and treated? Acta Paediatr 2008; 97(12):1605-10.
59. Venero C, Guadano-Ferraz A, Herrero AI, Nordström K, Manzano J, de Escobar GM, Bernal J, Vennström B. Anxiety, memory impairment, and locomotor dysfunction caused by a mutant thyroid hormone receptor α1 can be ameliorated by T3 treatment. Genes Dev 2005; 19:2152-63.
60. Wallis K, Sjogren M, van Hogerlinden M, Silberberg G, Fisahn A, Nordström K, Larsson L, Westerblad H, Morreale de Escobar G, Shupliakov O, Vennström B. Locomotor deficiencies and aberrant development of subtype-specific GABAergic interneurons caused by an unliganded thyroid hormone receptor α1. J Neurosci 2008; 28:1904-15.
61. Pilhatsch M, Winter C, Nordström K, Vennström B, Bauer M, Juckel G. Increased depressive behaviour in mice harboring the mutant thyroid hormone receptor alpha 1. Behav Brain Res 2010; 214(2):187-92.
62. Bao L, Roediger J, Park S, Fu L, Shi B, Cheng SY, Shi YB. Thyroid Hormone Receptor Alpha Mutations Lead to Epithelial Defects in the Adult Intestine in a Mouse Model of Resistance to Thyroid Hormone. Thyroid 2019; 29(3):439-48.
63. Pantos C, Xinaris C, Mourouzis I, Perimenis P, Politi E, Spanou D, Cokkinos DV. Thyroid hormone receptor alpha 1: a switch to cardiac cell "metamorphosis"? J Physiol Pharmacol 2008; 59(2):253-69.
64. Mittag, J. Cardiovascular consequences of a mutant thyroid hormone receptor α1. Eur J Endocrinol 2010; 6:51-54.
65. Makino A, Wang H, Scott BT, Yuan JX, Dillmann WH. Thyroid hormone receptor-α and vascular function. Am J Physiol Cell Physiol 2012; 302(9):C1346-52.
66. Marrif H, Schifman A, Stepanyan Z, Gillis MA, Calderone A, Weiss RE, Samarut J, Silva JE. Temperature homeostasis in transgenic mice lacking thyroid hormone receptor-alpha gene products. Endocrinology 2005; 146(7):2872-84.
67. Sjogren M, Alkemade A, Mittag J, Nordstrom K, Katz A, Rozell B, Westerblad H, Arner A, Vennström B. Hypermetabolism in mice caused by the central action of an unliganded thyroid hormone receptor alpha1. Embo J 2007; 26:4535-45.
68. Fein HG, Rivlin RS. Anemia in thyroid diseases. Med Clin North Am. 1975; 59:1133-45.
69. Kendrick TS, Payne CJ, Epis MR, Schneider JR, Leedman PJ, Klinken SP, Ingley E. Erythroid defects in TRalpha-/- mice. Blood 2008; 111(6):3245-8.
70. Angelin-Duclos C, Domenget C, Kolbus A, Beug H, Jurdic P, Samarut J. Thyroid hormone T3 acting through the thyroid hormone receptor is necessary for implementation of erythropoiesis in the neonatal spleen environment in the mouse. Development 2005; 132:925-34.

71. van Gucht ALM, Meima ME, Moran C, Agostini M, Tylki-Szymanska A, Krajewska MW, Chrzanowska K, Efthymiadou A, Chrysis D, Demir K, Visser WE, Visser TJ, Chatterjee K, van Dijk TB, Peeters RP. Anemia in Patients with Resistance to Thyroid Hormone α: A Role for Thyroid Hormone Receptor α in Human Erythropoiesis. J Clin Endocrinol Metab 2017; 102(9):3517-25.
72. van der Spek AH, Surovtseva OV, Aan S, Tool ATJ, van de Geer A, Demir K, van Gucht ALM, van Trotsenburg ASP, van den Berg TK, Fliers E, Boelen A. Increased circulating interleukin-8 in patients with resistance to thyroid hormone receptor α. Endocr Connect 2017; 6(8):731-40.
73. Goldman J, Matz R, Mortimer R, Freeman R. High elevations of creatine phosphokinase in hypothyroidism. An isoenzyme analysis. JAMA 1977; 238:325-6.
74. Boumaza H, Markossian S, Busi B, Rautureau GJP, Gauthier K, Elena-Herrmann B, Flamant F. Metabolomic Profiling of Body Fluids in Mouse Models Demonstrates that Nuclear Magnetic Resonance Is a Putative Diagnostic Tool for the Presence of Thyroid Hormone Receptor α1 Mutations. Thyroid 2019; 29(9):1327-35.
75. Persani L, Brabant G, Dattani M, Bonomi M, Feldt-Rasmussen U, Fliers E, Gruters A, Maiter D, Schoenmakers N, van Trotsenburg ASP. 2018 European Thyroid Association (ETA) Guidelines on the Diagnosis and Management of Central Hypothyroidism. Eur Thyroid J 2018;7(5):225-37.
76. Allan W, Herndon CN, Dudley FC. Some examples of the inheritance of mental deficiency: apparently sex-linked idiocy and microcephaly. Am J Ment Defic 1944; 48:325.
77. Schwartz CE, Stevenson RE. The MCT8 thyroid hormone transporter and Allan-Herndon-Dudley syndrome. Best Pract Res Clin Endocrinol Metab 2007; 21(2):307-21.
78. Anık A, Kersseboom S, Demir K, Catlı G, Yiş U, Böber E, van Mullem A, van Herebeek RE, Hız S, Abacı A, Visser TJ. Psychomotor retardation caused by a defective thyroid hormone transporter: report of two families with different MCT8 mutations. Horm Res Paediatr 2014; 82(4):261-71.
79. Herzovich V, Vaiani E, Marino R, Dratler G, Lazzati JM, Tilitzky S, Ramirez P, Iorcansky S, Rivarola MA, Belgorosky A. Unexpected peripheral markers of thyroid function in a patient with a novel mutation of the MCT8 thyroid hormone transporter gene. Horm Res 2007; 67(1):1-6.
80. Friesema EC, Grueters A, Biebermann H, Krude H, von Moers A, Reeser M, Barrett TG, Mancilla EE, Svensson J, Kester MH, Kuiper GG, Balkassmi S, Uitterlinden AG, Koehrle J, Rodien P, Halestrap AP, Visser TJ. Association between mutations in a thyroid hormone transporter and severe X-linked psychomotor retardation. Lancet 2004; 364(9443):1435-7.
81. Ocasio CA, Scanlan TS. Design and characterization of a thyroid hormone receptor alpha (TRalpha)-specific agonist. ACS Chem Biol 2006; 1:585-93.
82. Fozzatti L, Kim DW, Park JW, Willingham MC, Hollenberg AN, Cheng SY. Nuclear receptor corepressor (NCOR1) regulates in vivo actions of a mutated thyroid hormone receptor alpha. Proc Natl Acad Sci USA 2013; 110(19):7850–5.
83. Kim DW, Park JW, Willingham MC, Cheng SY. A histone deacetylase inhibitor improves hypothyroidism caused by a TRα1 mutant. Hum Mol Genet 2014; 23(10):2651–64.
84. Tan J, Cang S, Ma Y, Petrillo RL, Liu D. Novel histone deacetylase inhibitors in clinical trials as anti-cancer agents. J Hematol Oncol 2010; 3:5.
85. Wit JM, Kamp GA, Oostdijk W. Towards a Rational and Efficient Diagnostic Approach in Children Referred for Growth Failure to the General Paediatrician. Horm Res Paediatr 2019; 91(4):223-40.

Table 1. Genetic and laboratory findings in reported children with *THRA* variants (n=27). Except for two subjects, all of the patients with available data had at least one symptom or sign associated with hypothyroidism. Laboratory data were obtained before LT4 use in all subjects except patients 22 and 26, who were receiving LT4 treatment. When available, the data were given as exact values [high (H), normal (N), or low (L)] and relevant reference ranges in the original reports were given as footnotes.

Case	Variant	Type	Amino acid	Age (Years)	LT4-naive	fT3	TT3	rT3	fT4	TT4	TSH	CK	Hgb	Ref#
1	632A>G	Missense	D211G	1.5	Yes	N/A	3.6 (H)[b1]	0.09 (L)[c1]	9 (L)[d1]	110 (N)[e1]	4.4 (N)[f1]	N/A (N)[N/A]	6.2 (N)[h1]	23
2	776T>C	Missense	M259T	12	Yes	6.6 (H)[a1]	N/A	N/A	10.8 (L)[d2]	N/A	1.6 (N)[f2]	N/A	11.2 (L)[h2]	32
3	787G>T	Missense	A263S	2.6	Yes	7.28 (N)[a2]	3.65 (H)[b2]	0.31 (N)[c2]	16.4 (N)[d3]	85 (N)[e2]	2.1 (N)[f3]	236 (H)[g1]	11.6 (N)[h3]	24
4[#]	787G>T	Missense	A263S	7.4	Yes	7.96 (H)[a2]	3.46 (H)[b2]	0.27 (N)[c2]	17.6 (N)[d3]	98 (N)[e2]	1.4 (N)[f3]	218 (H)[g1]	10.8 (L)[h4]	24
5	787G>T	Missense	A263S	8.8	Yes	6.65 (N)[a2]	2.96 (H)[b2]	0.24 (N)[c2]	16.1 (N)[d3]	112 (N)[e2]	2.59 (N)[f3]	240 (H)[g1]	11.8 (N)[h4]	24
6[#]	787G>T	Missense	A263S	17	Yes	6.65 (N)[a2]	2.53 (H)[b2]	0.19 (L)[c2]	14.4 (N)[d3]	89 (N)[e2]	2.03 (N)[f3]	115 (N)[g1]	10.9 (L)[h5]	24
7	788C>T	Missense	A263V	17	Yes	7.6 (H)[a1]	N/A	<0.07 (L)[c3]	10 (N)[d4]	N/A	3.6 (N)[f4]	136 (N)[g2]	N/A (L)[N/A]	25
8	817A>G	Missense	T273A	2	Yes	9.6 (N)[a3]	N/A	N/A	6.8 (L)[d5]	N/A	2.09 (N)[f5]	N/A	9.3 (N/A)[N/A]	32
9	821T>C	Missense	L274P	11	Yes	N/A	N/A	N/A	9 (L)[d6]	N/A	2.4 (N)[f6]	N/A	N/A	25
10	871G>A	Missense	G291S	4	Yes	5.04 (H)[a4]	N/A	N/A	0.93 (N)[d7]	N/A	3.89 (N)[f4]	396 (H)[g3]	10.4 (L)[N/A]	29
11	1044G>T	Synonymous	A348A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	26
12	1053C>G	Missense	H351Q	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	26
13	1099C>A	Missense	L367M	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	26
14	1138del.4nt	Frameshift	C380fs387X	1.3	Yes	12.4 (H)[a2]	2.76 (H)[b2]	N/A	5.1 (L)[d3]	53 (L)[e2]	1.4 (N)[f3]	N/A	8.9 (L)[h3]	24
15	1144G>C	Missense	A382P	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	26
16	1150C>T	Missense	R384C	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	20
17	1151G>A	Missense	R384H	0.9	Yes	8.0 (H)[a2]	5.2 (H)[b2]	0.31 (N)[c2]	13.9 (N)[d3]	107 (N)[e2]	1.89 (N)[f3]	268 (H)[g1]	8.6 (L)[h3]	24

18	1176C>A	Nonsense	C392X	2	Yes	5.18 (H)[a5]	N/A	N/A	0.78 (N)[d8]	N/A	2.775 (N)[f7]	N/A (H)[N/A]	N/A (L)[N/A]	21
19	1176C>A	Nonsense	C392X	4	Yes	5.13 (N)[a6]	11.96 (N)[b3]	N/A	70 (N)[d9]	0.73 (N)[e3]	4.98 (N)[f8]	N/A	96 (L)[h6]	31
20	1183G>T	Nonsense	E395X	2	Yes	5.23 (H)[a7]	2.18 (N)[b4]	N/A	0.91 (L)[d10]	77.8 (N)[e4]	1.38 (N)[f9]	982 (H)[g4]	86 (L)[h7]	27, 28
21	Insert 1nt	Frameshift	F397fs406X	5	Yes	N/A	N/A (H)[N/A]	N/A (L)[N/A]	N/A (N)[N/A]	N/A (N)[N/A]	N/A (N)[N/A]	N/A	11.5 (L)[N/A]	16, 17
22	1193C>G	Missense	P398R	8	No	5.62 (N)[a8]	N/A	N/A	9.05 (L)[d11]	N/A	0.45 (N)[f7]	N/A (H)[N/A]	N/A (L)[N/A]	21
23	1202T>C	Missense	F401S	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	26
24	1207G>A	Missense	E403K	6	Yes	6.94 (N)[a9]	N/A	N/A	13.35 (N)[d12]	N/A	1.89 (N)[f7]	N/A (H)[N/A]	N/A (L)[N/A]	21
25	1207G>T	Nonsense	E403X	6	Yes	0.4 (N)[a10]	155 (N)[b5]	0.07 (L)[c4]	0.5 (L)[d13]	3.3 (L)[e5]	1.04 (N)[f10]	N/A	N/A	15
26	1207G>T	Nonsense	E403X	2.5	No	7.14 (H)[a11]	N/A	N/A	1.6 (H)[d14]	N/A	0.004 (L)[f7]	N/A (H)[N/A]	N/A (L)[N/A]	21
27	1213T>C	Missense	F405L	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	26

H high, N normal, L low, N/A Not available. [#] Asymptomatic, Reference ranges: Free T3 (fT3); [a1] 3.5-6.5 pmol/L, [a2] 3.8-7.6 pmol/L, [a3] 3.6-10.4 pmol/L, [a4] 2.3-4.2 pg/mL, [a5] 1.45-3.5 pg/mL, [a6] 1.78-5.6 ng/dL, [a7] 2.75-4.68 pg/mL, [a8] 3.88-8.02 pmol/L, [a9] 3.93-7.7 pmol/L, [a10] 0.3-0.5 ng/dL, [a11] 1.5-4 pg/mL. Total T3 (TT3); [b1] 1.3-2.7 nmol/L, [b2] 1.4-2.5 nmol/L, [b3] 7.0-22.0 ng/L, [b4] 0.99-2.27pg/mL, [b5] 130-221 ng/dL. Reverse T3 (rT3) (nmol/L); [c1] 0.11-0.44, [c2] 0.22-0.52, [c3] 0.12-0.36, [c4] 0.21-0.37. Free T4 (fT4); [d1] 10.0-23.0 pmol/L, [d2] 11.5-22.7 pmol/L, [d3] 11.0-25.0 pmol/L, [d4] 10-19.8 pmol/L, [d5] 7.5-21 pmol/L, [d6] 10.0-18.7 pmol/L, [d7] 0.89-1.76 ng/dL, [d8] 0.7-0.9 ng/dL, [d9] 50-230 pg/L, [d10] 1.2-1.73 ng/dL, [d11] 12.5-21.5 pmol/L, [d12] 12.6-21.5 pmol/L, [d13] 0.8-1.7 ng/dL, [d14] 0.6-1.4 ng/dL Total T4 (TT4); [e1] 70-150 nmol/L, [e2] 58-128 nmol/L, [e3] 0.45-1.54 µg/L, [e4] 51.8-122.5 ng/mL, [e5] 7.4-12.1 µg/dL. Thyroid-stimulating hormone (TSH) (mIU/L); [f1] 0.5-5.0, [f2] 0.51-4.9, [f3] 0.4-4.3, [f4] 0.35-5.5, [f5] 0.7-6.4, [f6] 0.4-5.5, [f7] 0.4-6.0, [f8] 0.25-7.31, [f9] 0.38-7.31, [f10] 0.8-6.2. Creatine Kinase (CK) (IU/L); [g1] 30-168, [g2] 47-163, [g3] 41-277, [g4] 25-225. Hemoglobin (Hgb); [h1] 6-9 mmol/L, [h2] 12-16 g/dL, [h3] >11 g/dL, [h4] >11.5 g/dL, [h5] >12 g/dL, [h6] 115-150 g/L, [h7] 110-140 g/L.

Table 2. Genetic and laboratory findings in reported adults with RTHα (n=13). All of the patients had at least one symptom or sign associated with hypothyroidism. The data of patients 6, 7, 8, and 10 were obtained after discontinuation of LT4, which was used for many years. Remaining laboratory data were obtained before LT4 use. When available, the data were given as exact values [high(H), normal(N), or low (L)] and relevant reference ranges in the original reports were given as footnotes.

Case	Variant	Type	Amino acid	Age (Years)	LT4-naive	fT3	TT3	rT3	fT4	TT4	TSH	CK	Hgb	Ref#
1	632A>G	Missense	D211G	N/A	Yes	N/A	2.25 (N)[b1]	0.12 (N)[c1]	10.1 (N)[d1]	85 (N)[e1]	1.6 (N)[f1]	N/A	7.3 (L)[h1]	23
2	767T>C	Missense	M256T	19	Yes	N/A	2.9 (H)[b2]	0.18 (L)[c2]	10.6 (L)[d2]	67 (N)[e2]	1.83 (N)[f2]	N/A	N/A	30
3	787G>T	Missense	A263S	31	Yes	5.94 (N)[a1]	2.51 (H)[b2]	0.27 (N)[c3]	16.1 (N)[d2]	87 (N)[e2]	0.95 (N)[f2]	87 (N)[g1]	9.6 (L)[h2]	24
4	787G>T	Missense	A263S	35	Yes	6.16 (N)[a1]	3.21 (H)[b2]	0.28 (N)[c3]	15.6 (N)[d2]	131 (H)[e2]	2.44 (N)[f2]	125 (N)[g1]	10.5 (L)[h2]	24
5	787G>T	Missense	A263S	55	Yes	5.96 (N)[a1]	2.57 (H)[b2]	0.28 (N)[c3]	13.6 (N)[d2]	98 (N)[e2]	1.58 (N)[f2]	125 (N)[g1]	13.5 (N)[h3]	24
6	788C>T	Missense	A263V	60	No	4.4 (N)[a2]	1.3 (N)[b3]	<50 (L)[c4]	9.4 (L)[d3]	60 (L)[e3]	4.6 (N)[f3]	364 (H)[g2]	120 (N)[h4]	19
7	788C>T	Missense	A263V	30	No	6.4 (N)[a2]	1.7 (N)[b3]	50 (L)[c4]	10.5 (N)[d3]	76.6 (N)[e3]	4.8 (N)[f3]	385 (H)[g2]	129 (L)[h5]	19
8	788C>T	Missense	A263V	26	No	6.8 (H)[a2]	2.1 (N)[b3]	<50 (L)[c4]	9.7 (L)[d3]	66.3 (L)[e3]	3.2 (N)[f3]	184 (N)[g2]	125 (L)[h5]	19
9	1075A>T	Missense	N359Y	25	Yes	0.4 (N)[a3]	N/A	0.17 (N)[c5]	0.8 (N)[d4]	N/A	0.343 (L)[f4]	55 (N)[g3]	10.8 (L)[h6]	22
10	c1144delG	Frameshift	A382PfsX7	45	No	4.9 (N)[a2]	1.7 (N)[b3]	10 (L)[c6]	10 (N)[d3]	85 (N)[e3]	5.8 (H)[f3]	387 (H)[g2]	12.7 (N)[h7]	18
11	1151G>A	Missense	R384H	35	Yes	6.3 (N)[a1]	3.32 (H)[b2]	0.2 (L)[c3]	13.6 (N)[d2]	80 (N)[e2]	2.51 (N)[f2]	125 (N)[g1]	11.2 (L)[h4]	24
12	Insert 1nt	Frameshift	F397fs406X	41	Yes	N/A	N/A (H)[N/A]	N/A (L)[N/A]	N/A (N)[N/A]	N/A (L)[N/A]	N/A (N)[N/A]	N/A	10 (L)[N/A]	16, 17
13	1207G>	Missens	E403K	39	Yes	2.2 (N)[a4]	N/A	N/A	76 (N)[d5]	N/A	2.4 (N)[f5]	N /A	N /A	21

	A	e												

H high, N normal, L low, N/A Not available. Reference ranges Free T3 (fT3); [a1] 3.8-7.6 pmol/L, [a2] 3.5-6.5 pmol/L, [a3] 0.2-0.4 ng/dL, [a4] 1.33-3.05 pg/mL. Total T3 (TT3) (nmol/L); [b1] 1.3-2.7, [b2] 1.4-2.5, [b3] 0.9-2.8. Reverse T3 (rT3); [c1] 0.11-0.44 nmol/L, [c2] 0.22-0.54 nmol/L, [c3] 0.22-0.52 nmol/L, [c4] 80-250 ng/L, [c5] 0.14-0.54 ng/mL, [c6] 11.0-32.0 ng/dL. **Free T4 (fT4);** [d1] 10.0-23.0 pmol/L, [d2] 11.0-25.0 pmol/L, [d3] 10.0-19.8 pmol/L, [d4] 0.7-1.2 ng/dL, [d5] 58-154 ng/dL. **Total T4 (TT4) (nmol/L);** [e1] 70-150, [e2] 58-128, [e3] 69-141. **Thyroid-stimulating hormone (TSH) (mIU/L);** [f1] 0.5-5.0, [f2] 0.4-4.3, [f3] 0.35-5.5, [f4] 0.4-3.6, [f5] 0.4-6.0. **Creatine Kinase (CK) (IU/L);** [g1] 30-168, [g2] 26-192, [g3] 20-180, [g4] 25-225. **Hemoglobin (Hgb);** [h1] 8.5-10.5 mmol/L, [h2] >12 g/dL, [h3] >13 g/dL, [h4] 115-160 g/L, [h5] 130-170 g/L, [h6] 12-16 g/dL, [h7] 11.5-16 g/dL.

Table 3. Summary of clinical features and underlying mechanism for RTHα. Pathophysiological mechanisms were observed from animal models, except for hematological findings.

Affected system	Pathophysiology	Clinical features
Skin	• Reduced DIO3 levels • Increased keratinocyte proliferation	• Coarse face • Macroglossia • Thickened skin • Skin tags
Skeletal	• Delayed ossification • Impaired bone remodeling • Reduced transcription of target genes such as growth hormone receptor, IGF-1 or its receptor and fibroblast growth factor receptor-1 or 3	• Short stature • Wormian bones • Cranial hyperostosis • Macrocephalia • Skeletal deformities • Delayed bone age • Delayed tooth eruption
Neurological and cognitive	• Impaired neuronal migration, synaptogenesis, maturation and myelination • Deficient differentiation of oligodendrocytes or glial cells • Abnormal evolution of GABAergic neurons	• Delayed milestones • Impaired cognitive functions • Motor incoordination • Slow movements • Dyspraxia

		• Speech delay • Dysarthric speech • Seizures • Anxiety • Autism spectrum disease
Gastrointestinal	• Shortened villi, increased differentiation in crypt cells and decreased stem cell proliferation • Decreased peristaltism	• Constipation
Cardiovascular	• Impaired cardiac myoblast differentiation • Weak cardiac contractions	• Bradycardia • Cardiomyopathy • Pericardial effusion
Metabolic	• Impaired facultative thermogenesis • Hyperphagia	• Obesity • Low metabolic rate • Hyperlipidemia
Hematological	• Compromised fetal and adult erythropoiesis • Slowed down differentiation of progenitor cells • Increased serum IL-8 levels	• Normocytic or macrocytic anemia

Figure 1. Thyroid function test results in previously untreated children and adults [derived from all available data in Table 1 (Cases 1-10, 14, 17-20, 24, and 25) and Table 2 (Cases 1-5, 9, 11, and 13)]. All of the data (x) was expressed relative to the relevant reference range with the following formula: (x - lower limit of normal range) / (upper limit of normal range - lower limit of normal range). Grey shaded areas indicated the normal range.

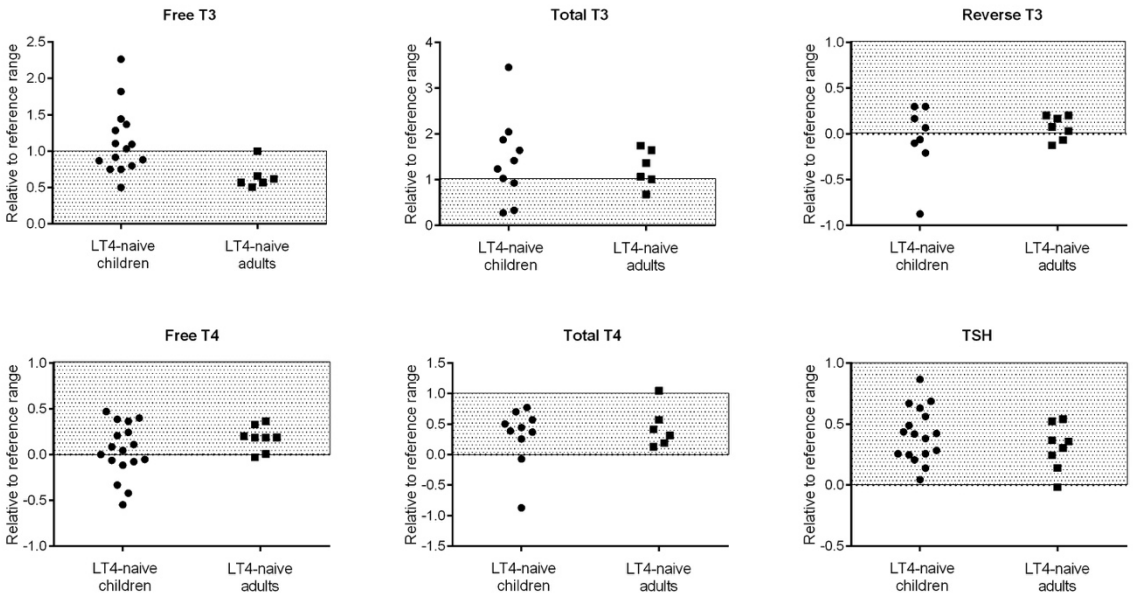


Figure 2. Classification of thyroid hormone profiles and peripheral indicators of hypothyroidism belonging to previously untreated children and adults. [derived from all available data in Table 1 (Cases 1-10, 14, 17-21, 24, and 25) and Table 2 (Cases 1-5, 9, and 11-13)].

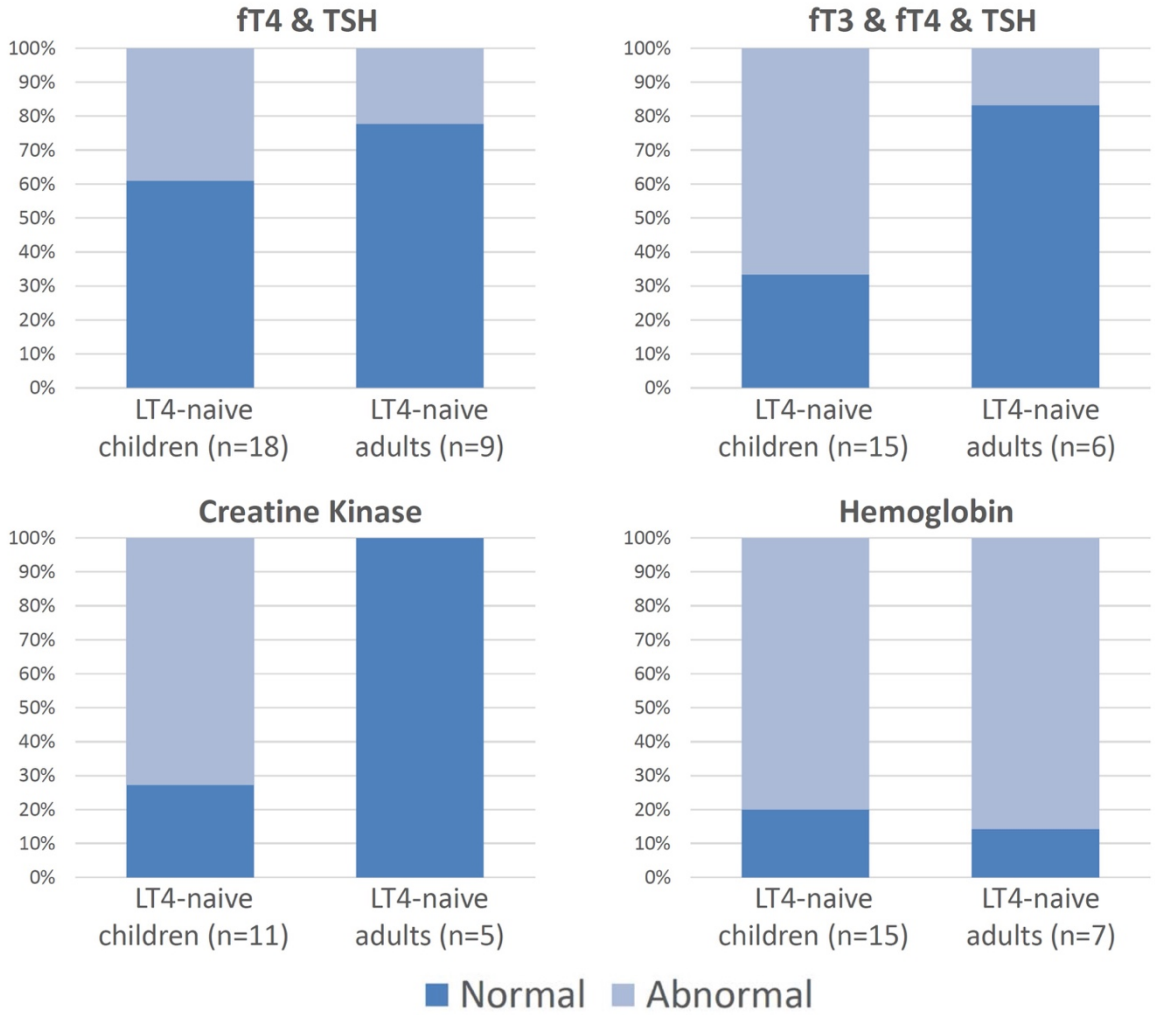


Figure 3. Numerical values of creatine kinase levels obtained from previously untreated children and adults with RTHα [derived from all available data in Table 1 (Cases 3-7, 10, 17, and 20) and Table 2 (Cases 3-5, 9, and 11)]. All of the data (x) was expressed relative to the relevant reference range with the following formula: (x - lower limit of normal range) / (upper limit of normal range - lower limit of normal range). Grey shaded area indicated the normal range.

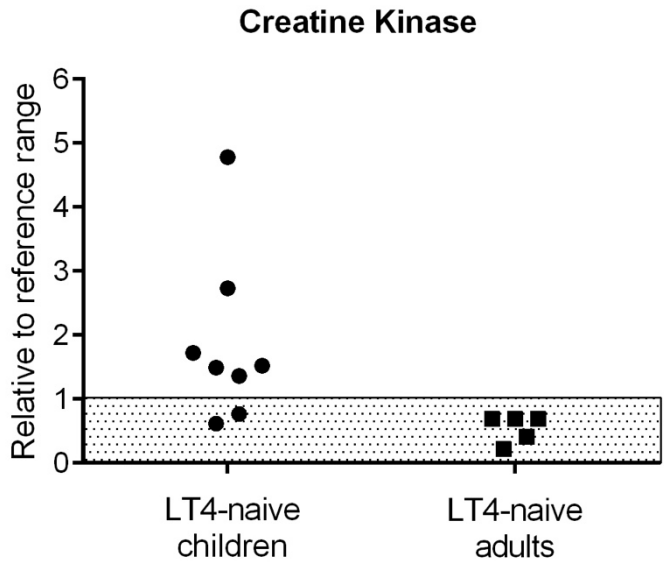
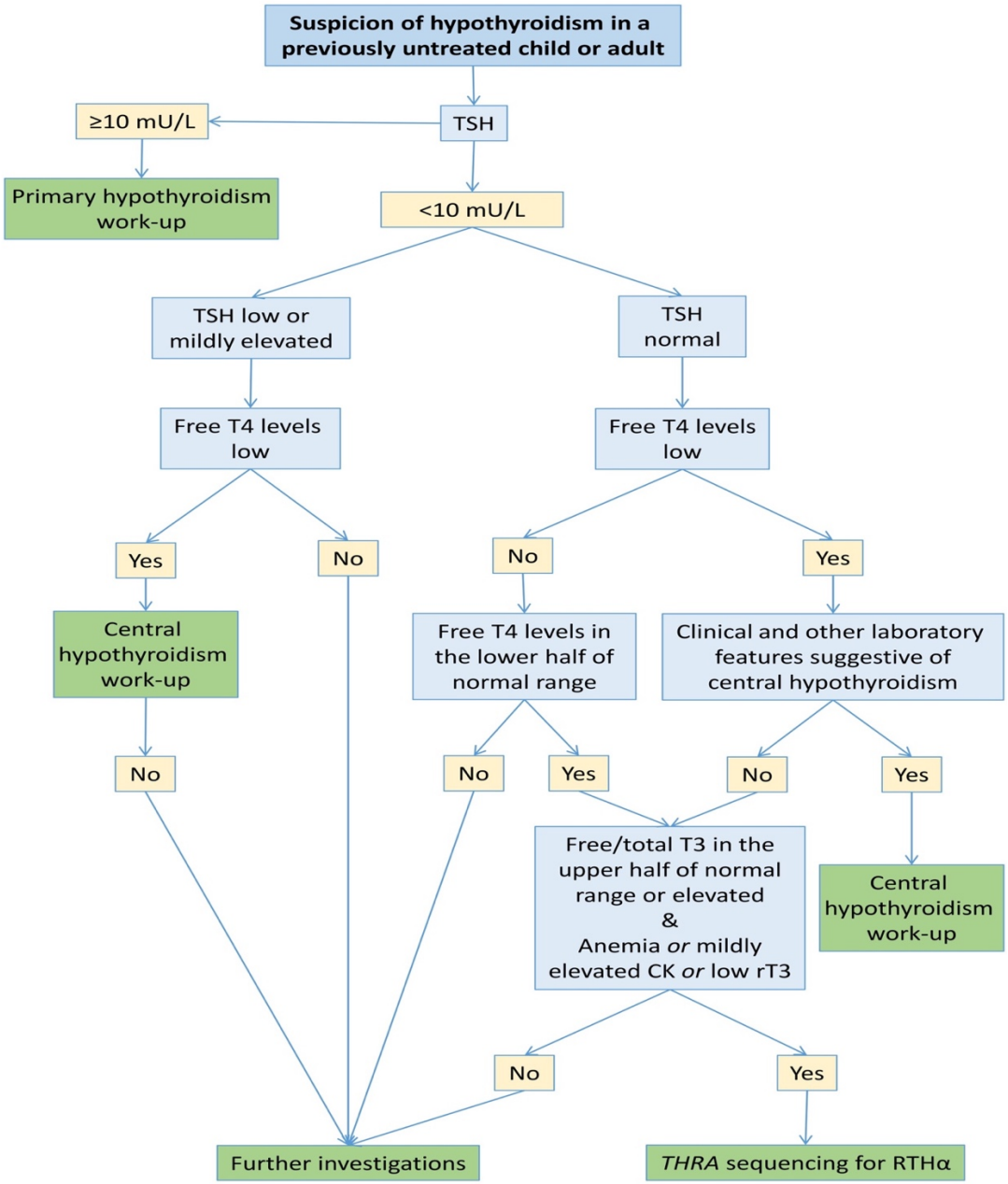


Figure 4. Algorithm for the differential diagnosis of hypothyroidism in previously untreated children and adults with particular emphasis on resistance to thyroid hormone alpha (RTHα).


Suspicion of hypothyroidism in a previously untreated child or adult
TSH
≥10 mU/L
Primary hypothyroidism work-up
<10 mU/L
TSH low or mildly elevated
TSH normal
Free T4 levels low
Free T4 levels low
Yes
No
No
Yes
Central hypothyroidism work-up
Free T4 levels in the lower half of normal range
Clinical and other laboratory features suggestive of central hypothyroidism
No
No
Yes
No
Yes
Free/total T3 in the upper half of normal range or elevated
&
Anemia *or* mildly elevated CK *or* low rT3
Central hypothyroidism work-up
No
Yes
Further investigations
THRA sequencing for RTHα