# Resistance to Thyroid Hormone and TSH Receptor Mutations

# 18

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**Abstract**

Resistance to thyroid hormone (RTH) is a syndrome characterized by variable tissue hyporesponsiveness to thyroid hormone throughout the body. Classically, patients come to attention for a variety of reasons including goiter, abnormal thyroid function tests (TFTs), or neonatal screening programs. Biochemically, the syndrome is characterized by elevated thyroid hormone values in the setting of non-suppressed thyrotropin (TSH) levels. In most patients, hyporesponsiveness occurs in both the hypothalamic and pituitary as well as peripheral tissues. Resistance in the hypothalamus and pituitary leads to elevated thyrotropin levels, which stimulate the thyroid gland to increase production of thyroid hormone; however, reduced action elsewhere results in (to a greater or lesser degree) compensated thyroid hormone hyporesponsiveness. In contrast, TSH resistance is caused by mutations in the TSH receptor, and is characterized by a range of symptoms, from euthyroid hyperthyrotropinemia to frank hypothyroidism.

**Keywords**

Thyroid hormone receptor • Resistance to thyroid hormone • Thyrotropin (TSH) • TSH receptor • Thyroid function tests • Mutation • Development

## Introduction

Resistance to thyroid hormone (RTH) is a syndrome characterized by variable tissue hyporesponsiveness to thyroid hormone throughout the body. Classically, patients come to attention for a variety of reasons including goiter, abnormal thyroid function tests (TFTs), or neonatal screening programs. Biochemically, the syndrome is characterized by elevated thyroid hormone values in the setting of non-suppressed thyrotropin (TSH) levels. In most patients, hyporesponsiveness occurs in both the hypothalamic and pituitary as well as peripheral tissues. Resistance in the hypothalamus and pituitary leads to elevated thyrotropin levels, which stimulate the thyroid gland to increase production of thyroid hormone; however, reduced action elsewhere results in (to a greater or lesser degree) compensated thyroid

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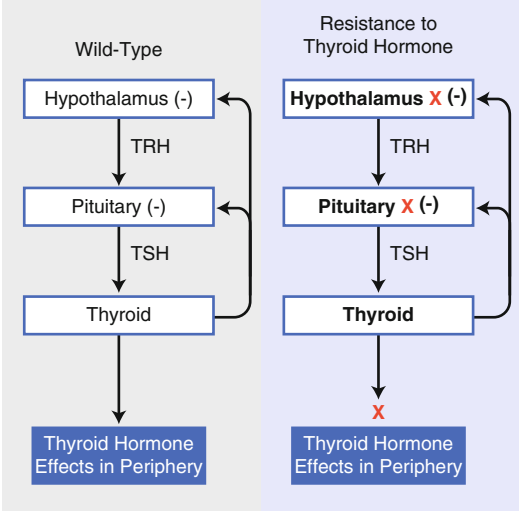


**Fig. 18.1** The hypothalamic–pituitary–thyroid axis in RTH patients. TRβ mutations or other (as yet undefined) defects in patients with RTH lead to reduced thyroid hormone responsiveness in the hypothalamus and pituitary, resulting in increased production of thyroid hormone. Impaired thyroid action elsewhere in the body results in the clinical phenotype seen in patients with RTH. However, increased thyroid hormone action on TRα receptors leads to selective tissue hyperthyroidism (e.g., in the heart conduction system)

hormone hyporesponsiveness (Fig. 18.1). Thus, affected individuals do not show classic signs and symptoms of myxedema, but instead exhibit delayed growth, hearing defects, attention-deficit hyperactivity disorder (ADHD), and other symptoms [1]. The majority of patients with RTH have autosomal dominant mutations of the thyroid hormone receptor-β (TRβ) gene. Patients have been identified from a wide range of races and ethnic groups; the exact geographic distribution of the disorder is unknown but it has been estimated that RTH occurs in about 1 case per 50,000 live births [2]. Therapeutic strategies for RTH are not well-defined and treatment (if any) must be individualized. Most studies of patients with RTH have been performed in adults, and approaches for the pediatric population may need to be deduced in the absence of firm data. In the past few years, additional syndromes of reduced sensitivity to thyroid hormone (but distinct from classic RTH) have been elucidated, and these will also be discussed below.

## Mechanisms of Resistance to Thyroid Hormone

The thyroid hormone receptor (TR) is a member of the nuclear hormone receptor (NHR) family of transcription factors. These proteins directly bind DNA to modulate gene transcription [3, 4]. NHRs contain a number of important domains: an N-terminal activation or AF-1 domain (A/B domain); a central DNA-binding domain (DBD); and a C-terminal ligand-binding domain (LBD) with ligand-dependent activation (AF-2) function. In addition to binding ligand, the LBD is also involved in the recruitment of key nuclear cofactors such as corepressors and coactivators.

TRs and other NHRs bind sequences within regulatory regions of genes; for the TR, these regions are termed thyroid hormone response elements (TREs) [5, 6]. When TRs bind to "positive" TREs (pTREs) in the presence of thyroid hormone, gene transcription is increased; in contrast, "negative" TREs (nTREs) are involved in thyroid hormone-mediated repression of transcription. Negative TREs have been identified in the promoters of TRH and TSH subunit genes [7–9]. The molecular events leading to thyroid hormone-mediated transcriptional repression remain unclear. In contrast, TR action on pTREs has been better characterized. On these genes, TRs are recruited to pTREs whether or not thyroid hormone is present (Fig. 18.2). In the absence of the active ligand triiodothyronine (T3), the TR binds nuclear proteins termed corepressors, including the nuclear corepressor protein (NCoR) and the silencing mediator of retinoid and thyroid hormone receptors (SMRT) [10–15]. These cofactors, in turn, recruit a protein complex with histone deacetylase function [16–18], leading to gene silencing. The binding of T3 leads to a conformational change in the TR, loss of corepressor binding, and subsequent recruitment of coactivators [19]. Coactivators stimulate gene expression by increasing the degree of histone acetylation, modulating interacts with general transcription factors, and other mechanisms [20–28]. More recently, rapid non-genomic actions of thyroid hormone have been identified (independent of

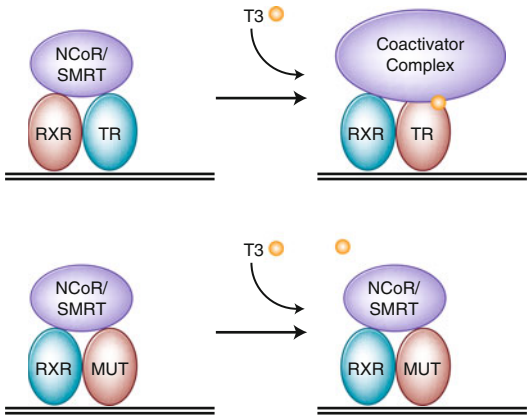


**Fig. 18.2** Role of abnormal TR—corepressor interactions in the pathogenesis of RTH. The thyroid hormone receptor (TR) binds DNA as a TR-retinoid X receptor (RXR) heterodimer (or potentially as a TR-TR homodimer). The presence of ligand (T3) results in a conformational change in the TR, leading to dissociation of corepressors (CoR) and subsequent recruitment of coactivators. Mutations of the TR that abolish T3 binding result in constitutive CoR recruitment and loss of T3-mediated stimulation of gene transcription

transcription) [3], though it is currently unclear how these effects relate to syndromes of RTH.

There are two major isoforms of the TR, termed TRα and TRβ, which are encoded on different chromosomes [29, 30]. The gene for TRα is located on chromosome 17; the gene for TRβ gene is located on chromosome 3. Additional isoforms of TRα and TRβ are generated by alternative splicing or differential promoter usage. Although TRα1 is a true thyroid hormone receptor, TRα2 is an alternatively spliced isoform that does not bind thyroid hormone. In contrast, TRβ1, TRβ2, and the more recently described TRβ3 isoform [31] all bind thyroid hormone and differ only in their proximal region. Additional truncated isoforms for both TRα [32] and TRβ [31] have been identified, but their functions in vivo remain unknown.

Mutations in the TRβ gene have been identified in many patients with RTH, and in the vast majority of cases, the syndrome is inherited in an autosomal dominant fashion. A subset of RTH patients, however, does not exhibit TRβ mutations [33]. These patients may have defects in other proteins involved in thyroid hormone action [34], but such mutations have not been identified [35]. This is an ongoing area of research, and novel mutations will likely be identified in the future. A recent search for mutations in the retinoid X receptor gamma (RXRγ) gene, though, was not successful [36]. It has been hypothesized that some RTH patients may exhibit mosaicism for TRβ mutations [37].

Mutations of TRβ that cause RTH generally cluster in three "hot spot" regions of the gene [38, 39]. Most of these mutations interfere with the binding of T3 to the receptor. In these cases, the mutant receptor strongly binds corepressors such as NCoR or SMRT even in the presence of T3 (Fig. 18.2). In a few patients, though, the defect is not with ligand binding per se, but with altered corepressor and/or coactivator recruitment [40, 41]. Interestingly, it has been shown that mutant TRs interfere with wild-type TR function, an effect has been termed "dominant-negative inhibition" [42, 43]. Recently, mouse models have clarified the role of the mutant TRs in the pathogenesis of RTH. Although complete knockout of TRβ produced mice with thyroid function tests consistent with RTH [44], "knock-in" of mutant TRs found in patients with RTH yielded mice with more severe resistance [45, 46]. Interestingly, knockout of TRα causes a syndrome of hypothyroidism with low TSH and growth arrest [47, 48]. Thus, a patient with a dominant-negative TRα mutation would be expected to have a different phenotype entirely.

RTH can be subdivided into generalized resistance to thyroid hormone (GRTH) and pituitary resistance to thyroid hormone (PRTH). In GRTH, the elevated thyroid hormone levels generated by resistance in the hypothalamus and pituitary have diminished activity in the periphery; thus, there is a variable degree of generalized resistance. In contrast, in PRTH (also called central resistance to thyroid hormone, or CRTH), there is resistance solely (or at least primarily) at the level of the hypothalamus and pituitary. This resistance leads to elevated levels of thyroid hormone, but in contrast to GRTH, sensitivity to thyroid hormone is maintained in peripheral tissues, causing thyrotoxicosis. Patients with GRTH frequently exhibit tachy-

cardia due to the high levels of thyroid hormone stimulating intact TRα1 receptors in the heart; thus, tachycardia should not be used to differentiate GRTH and PRTH. Certain groups do not recognize the existence of PRTH as a distinct clinical entity [49], arguing that the same mutations have been reported to cause both GRTH and PRTH [50]. However, a careful evaluation of clinical and biochemical indices in a patient with RTH suggested that PRTH may very well exist [51]. In addition, experiments have revealed that mutant TRs of patients with PRTH behave differently than TRs of patients with GRTH, particularly with respect to the TRβ2 isoform [52, 53]. A mouse model of the R429Q mutation (which has been reported to cause PRTH) showed that the mutant TR selectively interferes with negative regulation by thyroid hormone [54]. Another study identified differential recruitment of nuclear cofactors by a different TRβ mutation associated with PRTH [55].

## Clinical Presentation

The clinical presentation of RTH is variable (Table 18.1). The initial family described by Refetoff et al. [56] included an 8 1/2-year-old girl and a 12 1/2-year-old boy, both of whom were overall clinically euthyroid but exhibited goiter, deaf-mutism, stippled epiphyses on radiological skeletal survey, and elevated protein-bound iodine (PBI) levels. In contrast to most cases of RTH, this family was shown to have an autosomal recessive pattern of inheritance, and affected family members were later found to have a complete deletion of the TRβ allele [57]. The heterozygous parents were phenotypically normal, suggesting that a single wild-type TR (in the absence of a mutant TR) may be sufficient for thyroid hormone action. In contrast, most cases of RTH are inherited in an autosomal dominant fashion because mutant TRs exhibit dominant-negative inhibition over wild-type alleles.

Patients with RTH come to medical attention of a variety of reasons. Goiter is the presenting sign in about 38% of cases; less common reasons include learning disabilities, developmental delay, tachycardia, suspected thyrotoxicosis, and elevated thyroxine levels at birth [2]. Thyroid function tests are drawn, which reveal elevated thyroid hormone levels in the setting of a non-suppressed TSH (see "Diagnostic Guidelines" below). Infants with RTH may have congenital deafness, congenital nystagmus, neonatal jaundice, and hypotonia [1]. Patients with RTH may have an increased risk of developing autoimmune thyroid disease [58]. Individuals with RTH who have inappropriately underwent thyroidectomy or radioactive iodine treatment will exhibit signs and symptoms of hypothyroidism.

A National Institutes of Health study [59] evaluated a cohort of 42 RTH kindreds prospectively. There was autosomal dominant transmission in 22 kindreds, sporadic transmission in 14, and an unknown transmission in 6. A palpable goiter was identified in 74% of females and 53% of males. Attention-deficit hyperactivity disorder (ADHD) was present in 72% of the males and 43% of females. IQ was about 13 points lower in the patients with RTH compared to controls, and one-third of the patients had an IQ < 85. In contrast, only a few patients had actual mental retardation. Patients with RTH had a higher incidence of speech delay (24%), stuttering (18%), and hearing loss than controls. Although resting pulse was higher in patients with RTH, in this particular study, the correlation did not persist after adjustment for age (though it has been noted by other groups). Children with RTH exhibited delayed bone maturation. Bone age was delayed in 29% of patients, and 18% had short stature, though another study suggested that RTH is not associated with decreased final adult height [60].

As noted above, certain tissues demonstrate increased thyroid hormone-mediated effects in patients with RTH. This is presumably caused by thyroid hormone stimulation of TRα1 in these (TRα1-predominant) tissues. The classic example of this phenomenon is tachycardia, which has been reported in many patients with GRTH. More recently, Mitchell et al. reported that patients with RTH also exhibit increased energy expenditure, muscle mitochondrial uncoupling, and hyperphagia [61].

**Table 18.1** Clinical characteristics of RTH in children

| |
|---|
| *A. Physical exam* |
| 1. Goiter |
| 2. Tachycardia |
| 3. Short stature |
| 4. Low body weight |
| *B. Associated symptoms* |
| 1. Neurological |
| (a) Developmental delay |
| (b) Attention Deficit Hyperactivity Disorder (ADHD) |
| (c) Low IQ |
| 2. ENT |
| (a) Deafness |
| (b) Speech impediment |
| (c) Recurrent ear, nose, and throat infections |
| *C. Radiological findings* |
| 1. Delayed bone age |
| 2. Increased thyroid $^{123}$I uptake |

Clinical findings found in patients with resistance to thyroid hormone. Derived from data in Refs. [1, 59]

Findings of abnormal IQ and ADHD in patients with RTH suggest the importance of thyroid hormone in CNS development and function. Matochik et al. used positron emission tomography (PET) scans to study CNS activity in patients with RTH [62]. This study showed that RTH patients have higher cerebral metabolism in certain key areas of the central nervous system (CNS) during a continuous auditory discrimination task, including the anterior cingulate gyrus and the parietal lobe. While PET scanning techniques remain a research tool for RTH, these results suggest an important role for thyroid hormone in these CNS regions. A study of children with ADHD with and without coexisting RTH examined the role of thyroid hormone therapy (in this case, L-T3) in ADHD [63]. The majority of patients with RTH and ADHD improved when placed on T3 therapy, whereas patients with ADHD (in the absence of RTH) deteriorated or remained stable. Thus, ADHD in patients with RTH appears to be distinct from ADHD in patients without RTH [64].

While a number of unusual coexisting conditions in patients with RTH have been reported, some of these may have occurred by chance. These include a birdlike appearance of the face, various vertebral and other skeletal anomalies, short fourth metacarpals, patent ductus arteriosus, and noncommunicating hydrocephalus [1].

## Diagnostic Considerations

### Diagnosis in Children and Adults

The initial testing of a patient suspected to have RTH should include routine thyroid function tests. Patients with RTH have elevated free thyroid hormone levels in the setting of non-suppressed (normal or elevated) TSH levels. Other causes of "euthyroid hyperthyroxinemia" should be excluded (Table 18.2), including methodological laboratory artifacts due to the presence of heterophile antibodies [65]. Such patients may actually be hyperthyroid, with elevated thyroid hormone levels and (appropriately) suppressed TSH levels when measured accurately. This problem has been decreased, but not eliminated, with improvements in the TSH assay. Reevaluation of TSH levels after serial dilutions can be of help. Similarly, patients with autoimmune hypothyroidism occasionally exhibit falsely elevated thyroid hormone levels due to the presence of antibodies interfering with the measurement of T4 and/or T3.

Patients with defects in thyroid hormone-binding proteins, such as TBG, transthyretin, and albumin, can also exhibit abnormal levels of total T4 and T3. Euthyroid patients with TBG excess, which can be congenital or acquired (e.g., in pregnancy [66] and liver disease [67]), have elevated total T4 levels in the setting of a non-suppressed TSH. These patients, though, have normal free T4 levels, when measured directly or estimated based on THBR or T3RU. Familial dysalbuminemic hyperthyroxinemia (FDH) is a syndrome caused by the production of albumin variants with Arg-His or Arg-Pro mutations at codon 218 [68, 69]. These albumin variants have increased affinity for T4. Therefore, measurement of total serum T4 is elevated; correction of T4 based on T3RU or THBR may also yield abnormally high results. Free T4 levels are falsely elevated when measured by certain analog measurements, but a free T4 level measured by dialysis will be normal. Serum T3 levels are normal in FDH and exclude the diagnosis of RTH.

**Table 18.2** Causes of euthyroid hyperthyroxinemia

| |
|---|
| *1. Methodological artifacts* |
| (a) Antibodies to thyrotropin (TSH) |
| (b) Antibodies to thyroid hormones (T4, T3) |
| *2. Binding protein abnormalities* |
| (a) Acquired forms of increased TBG |
| – Estrogen use/pregnancy |
| – Liver disease |
| – Acute intermittent porphyria |
| – Other drugs (methadone, perphenazine, 5-FU) |
| (b) Inherited |
| – TBG excess |
| – Familial dysalbuminemic hyperthyroxinemia (FDH) |
| – Mutant transthyretin variants |
| *3. T4 to T3 conversion defects* |
| (a) Acquired |
| – Amiodarone |
| – Propranolol (high doses) |
| – Oral cholecystographic contrast agents |
| (b) Inherited (SBP2 mutations, possibly deidonase defects) |
| *4. Miscellaneous causes* |
| (a) Acute psychiatric illness |
| (b) High altitude |
| (c) Amphetamine use |
| (d) Thyroxine therapy |
| (e) Non-steady state conditions of thyroid hormone testing |
| *5. Resistance to thyroid hormone (RTH)* |

Causes of euthyroid hyperthyroxinemia in the differential diagnosis of resistance to thyroid hormone. Thyrotropin-secreting pituitary adenomas are not included, as they are generally associated with hyperthyroidism

Certain medications such as amiodarone [70] and propranolol (at high doses) inhibit T4 to T3 conversion. Euthyroid patients with T4 to T3 conversion defects may have elevated T4 levels and inappropriately normal TSH levels; however, these patients have normal TSH and T3 levels, excluding the diagnosis of RTH. Finally, a few other conditions such as acute psychiatric illness [71] can also cause abnormal thyroid function tests that can occasionally be confused with RTH (Table 18.2).

Once these various conditions are excluded, the diagnosis is generally one of RTH vs. thyrotroph adenoma [72]. Differentiation between these two disorders can be difficult, but the following guidelines can be used to distinguish them:

1. Symptoms of hyperthyroidism
   Thyrotroph adenomas secrete abnormal levels of TSH leading to hyperthyroidism. In contrast, GRTH patients generally have a variable degree of compensated thyroid hormone hyporesponsiveness. However, patients with PRTH are thyrotoxic, so the presence of thyrotoxicosis does not fully exclude RTH. Tachycardia is a common finding in patients with RTH (even GRTH), and it cannot be used as a screen for hyperthyroidism.
2. Alpha subunit measurement
   TSH is composed of alpha and beta subunits. The alpha subunit is common to other glycoprotein hormones such as luteinizing hormone (LH), follicle-stimulating hormone (FSH), and chorionic gonadotropin (CG). Patients with thyrotroph adenomas generally have higher alpha subunit levels than patients with RTH [72], though there is significant overlap.
3. Family history
   Thyroid function tests from relatives should be tested because RTH is an inherited condition. In contrast, thyrotroph adenomas are generally sporadic in nature. However, patients with RTH can harbor de novo mutations. Therefore, a lack of family history does not exclude a diagnosis of RTH.
4. MRI abnormalities
   Most patients with thyrotroph adenomas have macroadenomas that can be visualized by MRI at the time of diagnosis. However, with improved diagnostic accuracy, it may be possible to diagnose thyrotroph adenomas earlier in their clinical course. Furthermore, patients with RTH may have incidental pituitary adenomas, mimicking a thyrotroph adenoma [73]. However, the presence of a pituitary adenoma does make the diagnosis of thyrotroph adenoma more likely. In addition, pituitary adenomas may co-secrete multiple hormones; thus, other anterior pituitary hyperfunction

points to a more likely diagnosis of thyrotroph adenoma.

5. Thyroid ultrasonography
   A recent study used Doppler ultrasonography to determine whether thyroid blood flow distinguishes between RTH and thyrotroph adenomas [74]. These investigators showed that parameters of thyroid blood flow normalized in T3-treated RTH patients, but not in those with TSH-secreting adenomas.
6. TRH stimulation testing
   Patients with thyrotroph adenomas usually have a flat response of TSH in response to exogenous TRH, because TSH secretion is autonomous. In contrast, TSH levels generally rise after a TRH infusion in patients with RTH. Currently, TRH testing may not be feasible outside of research protocols due to the lack of availability of commercial TRH.
7. Reduced responsiveness to exogenous T3
   An effective method to confirm a diagnosis of RTH (at least GRTH) is to administer graded doses of T3 and measure a battery of thyroid hormone-responsive tests. Although patients with thyrotroph adenomas have impaired TSH responses to T3, they retain intact peripheral responses to T3. In contrast, patients with GRTH have impaired TSH and peripheral responses to exogenous T3. Unfortunately, patients with PRTH will also have reasonably intact peripheral responses to T3. Patients are generally admitted to a clinical research center for the duration of the protocol. A few protocols have been described, including one by Refetoff et al., where exogenous T3 is given in an escalating regimen [1]:
   (a) T3 25 μg po BID × 3 days.
   (b) T3 50 μg po BID × 3 days.
   (c) T3 100 μg po BID × 3 days.

   In pediatric patients, the middle 100-μg daily dose may be converted to 25 μg, for ages 1–3 (8–15 kg BW); 50 μg, for ages 4–9 (16–25 kg BW); and 75 μg, for ages 10–14 (26–45 kg BW), with the other doses altered accordingly. This type of approach has been successful, even in patients who have previously been inappropriately treated with radioiodine [75]. A variety of clinical parameters are measured, including weight, food intake, pulse, BMR, thyroid function tests, prolactin, thyroglobulin, cholesterol, triglycerides, creatine phosphokinase, ferritin, and SHBG. Alternatively, Safer et al. [51] used a mildly different protocol to evaluate a patient with PRTH. Adults were given T3 25 μg BID × 4 days, 50 μg BID × 4 days, and 100 μg BID × 4 days. Biochemical indices including TSH, ferritin, SHBG, ALT, AST, creatine phosphokinase, lactic dehydrogenase, total cholesterol, and fasting triglycerides were measured. Echocardiograms, sleeping heart rate measurements, ankle jerk relaxation time, and neuropsychiatric testing were also performed.
8. Thyroid hormone receptor mutations
   Most cases of RTH are associated with mutations in the TRβ gene. Ultimately, the most secure way to make a diagnosis of RTH is to demonstrate (a) elevated thyroid hormone levels in the setting of a non-suppressed TSH, (b) thyroid hormone hyporesponsiveness, and (c) a TRβ gene mutation.

## Neonatal Considerations

If a child is born to a parent with RTH with a known TR mutation, the most straightforward way to confirm or exclude the diagnosis in the infant is to sequence the known mutation. There are two other ways infants with RTH frequently come to medical attention: (a) symptoms consistent with RTH and (b) abnormal thyroid screening tests. Infants with RTH may have congenital deafness, congenital nystagmus, neonatal jaundice, and hypotonia. In addition, screening programs that are in place to identify infants with congenital hypothyroidism occasionally identify RTH instead. A fetus with suspected RTH can be tested for TR mutations by chorionic villus sampling and DNA analysis [76], though the benefits of making the diagnosis at this stage of development have not been clearly established.

## Therapy

No specific therapy is available to correct the underlying defect in RTH. Frequently, patients with RTH are in a clinical state of compensated thyroid hormone hyporesponsiveness. In these patients, no specific therapy is indicated. In those few patients who have greater peripheral hyporesponsiveness and thus clinical hypothyroidism, treatment with thyroid hormone (e.g., levothyroxine) may be considered. If used, the specific dosage must be individualized based on markers of thyroid hormone action (such as SHBG, cholesterol, ferritin, BMR, and bone density) [50]. The use of TRIAC (3,5,3′-triiodothyroacetic acid), a thyroid hormone analog with relative specificity toward the TRβ receptor [77, 78], has been advocated for use in patients with RTH, but its specific role has not been clearly defined. D-Thyroxine has also been used [79], though one study suggested it was less effective than TRIAC [80]. Novel TR analogs hopefully will be developed that activate mutant receptors [81]. In sum, therapy (or lack thereof) must be individualized for each patient. Of course, for patients who have had their thyroid glands inappropriately ablated for misdiagnosed hyperthyroidism, treatment with thyroid hormone will be necessary.

In patients with PRTH, beta blockers have been used to control symptoms; the use of antithyroid drugs in this situation is controversial, and these medications are not indicated in patients with GRTH. Agents that have been used to decrease TSH levels include somatostatin analogs and bromocriptine, but these have had only limited success.

The care of RTH patients during pregnancy needs to be individualized as well and depends on the genotype of both the fetus and mother [82]. High miscarriage rates of wild-type fetuses of pregnant RTH mothers has been suggested to be due to high circulating levels of thyroid hormone [83]. A prenatal diagnosis of RTH was made [76] in a 29-year-old pregnant woman with at 17 weeks gestation. The fetus and mother were both found to harbor the identical TRβ mutation (T337A), and the pregnant woman was treated with TRIAC with beneficial effects on maternal symptoms and fetal goiter size. Cordocentesis was performed to evaluate effects of the medication on fetal thyroid function tests. However, an accompanying editorial to the report [50] points out some potential dangers of this approach, since cordocentesis led to the need for emergency C-section.

In children with RTH, special care should be directed toward issues of growth and mental development. Patients with delayed bone age may be candidates for therapy. One approach is to consider treatment in children with the following signs and symptoms: (a) elevated serum TSH levels, (b) unexplained failure to thrive, (c) unexplained seizures, (d) developmental delay, and (e) history of growth or mental retardation in other affected members of the family [50]. As noted above, patients with RTH and coexisting ADHD may improve when treated with thyroid hormone [63]. In any case, patients who require treatment should be followed closely, with careful evaluation of growth, bone age, and thyroid-responsive biochemical indices.

## Additional Thyroid Hormone Insensitivity Syndromes

In recent years, additional genetic syndromes have been identified that are associated with decreased thyroid hormone sensitivity in one form or another (but distinct from RTH). Such syndromes generally involve defects in thyroid hormone metabolism or transport.

For many years, it was thought that thyroid hormone diffused passively through cell membranes. We now know that thyroid hormone is taken up into cells by a variety of transporter proteins [84]. One of these transporters is MCT8 and its gene is located on the X chromosome. Multiple patients with MCT8 mutations have now been identified that exhibit X-linked mental retardation and hypotonia presenting in infancy or childhood [85, 86]. In these patients, serum T3 levels are elevated, free T4 levels are low, and TSH is normal or mildly increased. The severe CNS symptoms are due at least in part to impaired transport of thyroid hormone in the brain.

Although brain T3 levels have been documented to be low, liver T3 levels are high [87], so that patients have a complex mix of hypothyroid and hyperthyroid symptoms. While current therapeutic options are limited to supportive measures, a recent study identified a thyroid hormone analog that did not require MCT8 for transport and may represent a novel modality for patients suffering from this syndrome [88].

While mutations in deiodinase genes have not been identified, a recently described syndrome identified mutations in selenocysteine insertion sequence-binding protein 2 (SECISBP2 or SBP2). SBP is involved in the incorporation of the unusual amino acid selenocysteine to generate selenoproteins. Since deiodinase enzymes are selenoproteins, these recessive mutations result in abnormalities in thyroid hormone metabolism. Affected patients exhibit low T3 levels, high T4 levels, and normal or slightly elevated TSH levels [89, 90]. Recently, other kindreds with SBP2 mutations were found to have coexisting azoospermia, axial muscular dystrophy, photosensitivity, abnormal immune function, and insulin sensitivity [91], suggesting that SBP2 mutations produce a complex, systemic selenoprotein deficiency syndrome.

## TSH Receptor Mutations

### Introduction

Thyrotropin (TSH) is a member of the glycoprotein family of hormone secreted by the anterior pituitary, along with luteinizing hormone (LH) and follicle-stimulating hormone (FSH) [92]. These hormones along with chorionic gonadotropin consist of noncovalently linked α and β subunits, with linked carbohydrate chains. While the β subunit of each hormone is unique, all share a common α subunit. TSH stimulates the growth and function of thyroid follicular cells, leading to the production of thyroid hormone. Thus, resistance to TSH ranges from a compensated state of euthyroid hyperthyrotropinemia to frank hypothyroidism. The first report of a patient with resistance to the biological properties of TSH was in 1968 [93], but it was not until 1995 that the first patient with a TSH receptor mutation was firmly documented [94].

### Mechanisms of Disease and Clinical Presentation of TSH Resistance

In 1995, Sunthornthepvarakul et al. documented the first case of a TSH receptor mutation leading to TSH resistance [94]. The index case was an infant born to unrelated parents found to have an elevated TSH level on routine neonatal screening. Two siblings were also found to have high TSH levels and normal thyroid hormone levels. All were clinically euthyroid and found to be compound heterozygotes for mutations in exon 6 of the TSH receptor corresponding to a region in the TSH extracellular domain [94]. In vitro data confirmed the mutant receptors exhibited decreased biological activity. Since that time, a number of other patients have been identified with TSH receptor mutations and TSH resistance, though additional patients have been identified without identifiable mutations. Most patients with TSH receptor mutations are either homozygotes or compound heterozygotes.

The TSH receptor is a transmembrane G-coupled receptor (Fig. 18.3). It contains a large extracellular domain with three regions—the middle of these regions (approximately amino acids 58–288) contains the most significant homology to FSH and LH receptors [95]. The extracellular domain may inhibit constitutive activity of the receptor [96]. The carboxy-terminal portion of the TSH receptor includes the transmembrane domain, which spans the plasma membrane seven times, and an 82 amino acid cytoplasmic tail [96]. The gene encoding the TSH receptor has been localized to chromosome 14q31 [97, 98].

There are two general modes of presentation for patients with loss-of-function germline TSH receptor mutations. The first is similar to the family identified by Sunthornthepvarakul et al. [94]. In these patients, high TSH levels are necessary to overcome partial TSH resistance, and patients remain euthyroid (compensated euthyroid

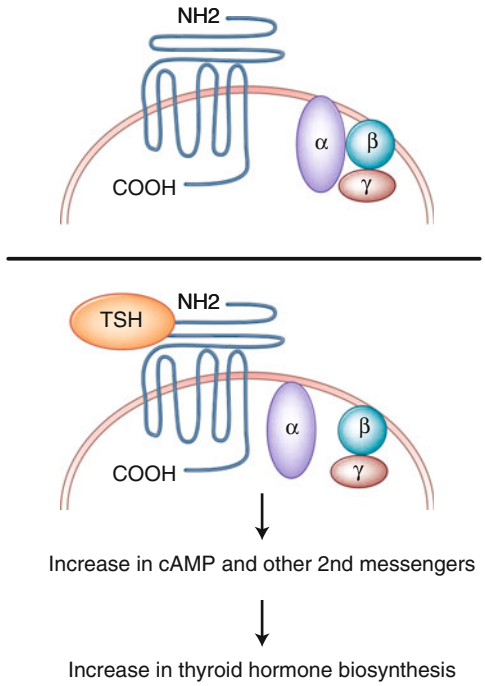


**Fig. 18.3** Schematic diagram of the TSH receptor. The TSH receptor is composed of an N-terminal extracellular domain, a transmembrane region (which spans the plasma membrane seven times), and a cytoplasmic tail. Stimulation of the TSH receptor leads to G-protein dissociation and activation

hyperthyrotropinemia). Four additional families with these clinical characteristics were identified by de Roux et al. [99]. One patient had a homozygous mutation in codon 162 of the TSH receptor; the other three were compound heterozygotes. Interestingly, one of the mutations (C390W) caused loss of TSH binding, whereas another (D410N) resulted in normal TSH binding but an inability to activate the second messenger adenylate cyclase. Mutations affecting signal transduction were also found in extracellular (D410N) and intracellular (F525L) domains [99]. Additional mutations have been identified from patients with euthyroid hyperthyrotropinemia [100, 101].

In contrast, other TSH receptor mutations cause more extreme hormone resistance. Patients with these mutations present with hypothyroidism and may be identified by neonatal screening. Abramowicz et al. reported two such patients, a brother and sister, who were diagnosed with congenital hypothyroidism [102]. Ultrasound evaluation revealed hypoplastic thyroid glands. A homozygous mutation of the TSH receptor in the fourth transmembrane domain (A553T) was identified; the parents and unaffected siblings were heterozygous for the same mutation. In vitro analysis suggested that there was decreased expression of the mutant receptor at the cell surface [102]. Severely affected patients have been identified by other groups as well [103–105].

Not all patients with resistance to TSH have mutations in the TSH receptor [106]. Patients with pseudohypoparathyroidism caused by mutations in GNAS may exhibit resistance to a variety of hormones including TSH [107]. Mutations in transcription factors involved in thyroid gland development such as Pax8 [108] and TITF1 (Nkx2.1) [109] have been reported to cause resistance to TSH. Finally, Grasberger et al. identified multiple kindreds with resistance to TSH inherited in an autosomal dominant fashion without identifiable mutations [110].

## Diagnostic Considerations and Therapy

Mild TSH resistance (euthyroid hyperthyrotropinemia) is easily confused with subclinical hypothyroidism, since both present with elevated TSH levels in the setting of normal free thyroid hormone levels. Most cases of subclinical hypothyroidism are due to underlying autoimmune thyroid disease, which is generally absent in resistance to TSH. Patients with more severe TSH resistance present with thyroid function tests consistent with primary hypothyroidism. Patients with resistance to TSH, however, do not have a goiter and the disorder is usually (but not always) inherited in an autosomal recessive pattern.

TSH resistance may be detected by neonatal screening programs. Since congenital hypothyroidism is not generally inherited, a significant family history of congenital hypothyroidism is suggestive for TSH resistance. A recent study in Japan of congenital hypothyroid infants found that 4.3% had biallelic TSH receptor mutations; the authors estimated that the frequency of TSH receptor heterozygous carriers to be 1 in 172 in that population [111]. Thus, the prevalence of TSH resistance may be higher than previously appreciated.

Patients with mild TSH resistance and mild hyperthyrotropinemia are clinically euthyroid and do not require treatment, although they should receive genetic counseling. Patients with more severe TSH resistance and frank hypothyroidism are treated with levothyroxine.

## Conclusion

Hormone resistance leading to thyroid dysfunction occurs at multiple levels of the hypothalamic–pituitary–thyroid axis. Care of patients with RTH must be individualized, and the endocrine status of the patient must be determined rigorously. In children, special attention must be paid to growth, bone development, and mental development. Further studies in children should be performed so that medical care can be optimized in these patients. RTH is usually caused by autosomal dominant mutations of the TRβ gene. In contrast, resistance to TSH is usually caused by autosomal recessive mutations in the TSH receptor gene. However, patients with both disorders have been identified without mutations. These patients probably harbor mutations in other important endocrine genes. Further evaluation of these patients will be important not only to optimize their medical care but also to gain fundamental insights into the mechanisms of action of thyroid hormone, TSH, and other hormones.

## Note Added in Proof

Recently, patients with mutations in TR alpha have also been described [112]. This new syndrome is characterized by cognitive deficits, constipation, and short stature. The index patient exhibited normal levels of TSH, mildly low free T4, and highnormal T3.

## References

1. Refetoff S, Weiss RE, Usala SJ. The syndromes of resistance to thyroid hormone. Endocr Rev. 1993;14:348–99.
2. Refetoff S. Resistance to thyroid hormone. In: Braverman LE, Utiger RD, editors. Werner and Ingbar's the thyroid: a fundamental and clinical text. 8th ed. Philadelphia, PA: Lippincott, Williams, and Wilkins; 2000. p. 1028–43.
3. Cheng SY, Leonard JL, Davis PJ. Molecular aspects of thyroid hormone actions. Endocr Rev. 2010; 31(2):139–70.
4. Mangelsdorf DJ, Thummel C, Beato M, et al. Overview: the nuclear receptor superfamily: the second decade. Cell. 1995;83:835–40.
5. Katz RW, Subauste JS, Koenig RJ. The interplay of half-site sequence and spacing on the activity of direct repeat thyroid hormone response elements. J Biol Chem. 1995;270(10):5238–42.
6. Umesono K, Murakami KK, Thompson CC, Evans RM. Direct repeats as selective response elements for the thyroid hormone, retinoic acid and vitamin D3 receptors. Cell. 1991;65:1255–66.
7. Bodenner DL, Mrocynski MA, Weintraub BD, Radovick S, Wondisford FE. A detailed functional and structural analysis of a major thyroid inhibitory element in the human thyrotropin β-subunit gene. J Biol Chem. 1991;266:21666–73.
8. Hollenberg AN, Monden T, Flynn TR, Boers M-E, Cohen O, Wondisford FE. The human thyrotropin-releasing hormone gene is regulated by thyroid hormone through two distinct classes of negative thyroid hormone response elements. Mol Endocrinol. 1995;10:540–50.
9. Tomie-Canie M, Day D, Samuels HH, Freedberg IM, Blumenberg M. Novel regulation of keratin gene expression by thyroid hormone and retinoid receptors. J Biol Chem. 1996;271(3):1416–23.
10. Chen JD, Evans RM. A transcriptional co-repressor that interacts with nuclear hormone receptors [see comments]. Nature. 1995;377(6548):454–7.
11. Horlein AJ, Naar AM, Heinzel T, et al. Ligand-independent repression by the thyroid hormone receptor mediated by a nuclear receptor co-repressor [see comments]. Nature. 1995;377(6548):397–404.
12. Ordentlich P, Downes M, Xie W, Genin A, Spinner NB, Evans RM. Unique forms of human and mouse nuclear receptor corepressor SMRT. Proc Natl Acad Sci USA. 1999;96(6):2639–44.
13. Park EJ, Schroen DJ, Yang M, Li H, Li L, Chen JD. SMRTe, a silencing mediator for retinoid and thyroid hormone receptors-extended isoform that is more related to the nuclear receptor corepressor. Proc Natl Acad Sci USA. 1999;96(7):3519–24.
14. Sande S, Privalsky ML. Identification of TRACs (T3 receptor-associating cofactors), a family of cofactors that associate with and modulate the activity of, nuclear hormone receptors. Mol Endocrinol. 1996;10: 813–25.
15. Seol W, Choi HS, Moore DD. Isolation of proteins that interact specifically with the retinoid X receptor: two novel orphan nuclear receptors. Mol Endocrinol. 1995;9:72–85.
16. Alland L, Muhle R, Hou HJ, et al. Role for N-CoR and histone deacetylase in Sin3-mediated transcriptional repression. Nature. 1997;387:49–55.
17. Heinzel T, Lavinsky RM, Mullen TM, et al. A complex containing N-CoR, mSin3 and histone deacetylase

mediates transcriptional repression [see comments]. Nature. 1997;387(6628):43–8.
18. Nagy L, Kao H-K, Chakravarti D, et al. Nuclear receptor repression mediated by a complex containing SMRT, mSin3A, and histone deacetylase. Cell. 1997;89:373–80.
19. Feng W, Ribeiro RCJ, Wagner RL, et al. Hormone-dependent coactivator binding to a hydrophobic cleft on nuclear receptors. Science. 1998;280:1747–9.
20. Anzick SL, Kononen J, Walker RL, et al. AIB1, a steroid receptor coactivator amplified in breast and ovarian cancer. Nature. 1997;277:965–8.
21. Cavailles V, Dauvois S, L'Horset F, et al. Nuclear factor RIP140 modulates transcriptional activation by the estrogen receptor. EMBO J. 1995;14:3741–51.
22. Chen H, Lin RJ, Schlitz RL, et al. Nuclear receptor coactivator ACTR is a novel histone acetyltransferase and forms a multimeric activation complex with P/CAF and CBP/p300. Cell. 1997;90:569–80.
23. Kamei Y, Xu L, Heinzel T, et al. A CBP integrator complex mediates transcriptional activation and AP-1 inhibition by nuclear receptors. Cell. 1996;85(3): 403–14.
24. Monden T, Wondisford FE, Hollenberg AN. Isolation and characterization of a novel ligand-dependent thyroid hormone receptor-coactivating protein. J Biol Chem. 1997;272(47):29834–41.
25. Onate SA, Tsai SY, Tsai M-J, O'Malley BW. Sequence and characterization of a coactivator for the steroid hormone receptor superfamily. Science. 1995;270:1354–7.
26. Takeshita A, Yen PM, Misiti S, Cardona GR, Liu Y, Chin WW. Molecular cloning and properties of a full-length putative thyroid hormone receptor coactivator. Endocrinology. 1996;137:3594–7.
27. Torchia J, Rose DW, Inostroza J, et al. The transcriptional co-activator p/CIP binds CBP and mediates nuclear receptor function. Nature. 1997;387:677–84.
28. Voegel JJ, Heine MJS, Zechel C, Chambon P, Gronemeyer H. TIF2, a 160 KD transcriptional mediator for the ligand-dependent activation function AF-2 of nuclear receptors. EMBO J. 1996;15:3667–75.
29. Sap J, Munoz A, Damm K, et al. The c-erb-A gene protein is a high-affinity receptor for thyroid hormone. Nature. 1986;324:635–40.
30. Weinberger C, Thompson CC, Ong ES, Lebo R, Gruol DJ, Evans RM. The c-erb-A gene encodes a thyroid hormone receptor. Nature. 1986;324:641–6.
31. Williams GR. Cloning and characterization of two novel thyroid hormone receptor beta isoforms. Mol Cell Biol. 2000;20:8329–42.
32. Plateroti M, Gauthier K, Domon-Dell C, Freund JN, Samarut J, Chassande O. Functional interference between thyroid hormone receptor alpha (TRalpha) and natural truncated TRDeltaalpha isoforms in the control of intestine development. Mol Cell Biol. 2001;21(14):4761–72.
33. Weiss RE. "They have ears but do not hear" (Psalms 135:17): non-thyroid hormone receptor beta (non-TRbeta) resistance to thyroid hormone. Thyroid. 2008;18(1):3–5.
34. Weiss RE, Hayashi Y, Nagaya T, et al. Dominant inheritance of resistance to thyroid hormone not linked to defects in the thyroid hormone receptor α or β genes may be due to a defective cofactor. J Clin Endocrinol Metab. 1996;81:4196–203.
35. Reutrakal S, Sadow PM, Pannain S, et al. Search for abnormalities of nuclear corepressors, coactivators, and a coregulator in families with resistance to thyroid hormone without mutations in thyroid hormone receptor β or α genes. J Clin Endocrinol Metab. 2000;85:3609–17.
36. Romeo S, Menzaghi C, Bruno R, et al. Search for genetic variants in the retinoid X receptor-gamma-gene by polymerase chain reaction-single-strand conformation polymorphism in patients with resistance to thyroid hormone without mutations in thyroid hormone receptor beta gene. Thyroid. 2004;14(5): 355–8.
37. Mamanasiri S, Yesil S, Dumitrescu AM, et al. Mosaicism of a thyroid hormone receptor-beta gene mutation in resistance to thyroid hormone. J Clin Endocrinol Metab. 2006;91(9):3471–7.
38. Collingwood TN, Wagner R, Matthews CH, et al. A role for helix 3 of the TRb ligand-binding domain in coactivator recruitment identified by characterization of a third cluster of mutations in resistance to thyroid hormone. EMBO J. 1998;17:4760–70.
39. Safer JD, Cohen RN, Hollenberg AN, Wondisford FE. Defective release of corepressor by hinge mutants of the thyroid hormone receptor found in patients with resistance to thyroid hormone. J Biol Chem. 1998;273(46):30175–82.
40. Collingwood TN, Rajanayagam O, Adams M, et al. A natural transactivation mutation in the thyroid hormone beta receptor: impaired interaction with putative transcriptional mediators. Proc Natl Acad Sci USA. 1997;94(1):248–53.
41. Yoh SM, Chatterjee VK, Privalsky ML. Thyroid hormone resistance syndrome manifests as an aberrant interaction between mutant T3 receptors and transcriptional corepressors. Mol Endocrinol. 1997;11(4):470–80.
42. Nagaya T, Jameson JL. Thyroid hormone receptor dimerization is required for dominant negative inhibition by mutations that cause thyroid hormone resistance. J Biol Chem. 1993;268:15766–71.
43. Nagaya T, Madison LD, Jameson JL. Thyroid hormone receptor mutants that cause resistance to thyroid hormone. J Biol Chem. 1992;267:13014–9.
44. Forrest D, Hanebuth E, Smeyne RJ, et al. Recessive resistance to thyroid hormone in mice lacking thyroid hormone receptor beta: evidence for tissue-specific modulation of receptor function. EMBO J. 1996;15(12):3006–15.
45. Hashimoto K, Curty FH, Borges PB, et al. An unliganded thyroid hormone receptor causes severe neurological dysfunction. Proc Natl Acad Sci USA. 2001;98:3998–4003.

46. Kaneshige M, Kaneshige K, Xhu X, et al. Mice with a targeted mutation in the thyroid hormone beta receptor gene exhibit impaired growth and resistance to thyroid hormone. Proc Natl Acad Sci USA. 2000;97:13209–14.
47. Fraichard A, Chassande O, Plateroti M, et al. The T3R alpha gene encoding a thyroid hormone receptor is essential for post-natal development and thyroid hormone production. EMBO J. 1997;16(14): 4412–20.
48. Wikstrom L, Johansson C, Salto C, et al. Abnormal heart rate and body temperature in mice lacking thyroid hormone receptor alpha 1. EMBO J. 1998;17(2): 455–61.
49. 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.
50. Weiss RE, Refetoff S. Editorial: treatment of resistance to thyroid hormone—primum non nocere. J Clin Endocrinol Metab. 1999;84:401–3.
51. Safer JD, O'Connor MG, Colan SD, Srinivasan S, Tollin SR, Wondisford FE. The thyroid hormone receptor-β mutation R383H is associated with isolated central resistance to thyroid hormone. J Clin Endocrinol Metab. 1999;84:3099–109.
52. Safer JD, Langlois MF, Cohen R, et al. Isoform variable action among thyroid hormone receptor mutants provides insight into pituitary resistance to thyroid hormone. Mol Endocrinol. 1997;11:16–26.
53. Wan W, Farboud B, Privalsky ML. Pituitary resistance to thyroid hormone syndrome is associated with T3 receptor mutants that selectively impair beta2 isoform function. Mol Endocrinol. 2005;19(6): 1529–42.
54. Machado DS, Sabet A, Santiago LA, et al. A thyroid hormone receptor mutation that dissociates thyroid hormone regulation of gene expression in vivo. Proc Natl Acad Sci USA. 2009;106(23):9441–6.
55. Wu SY, Cohen RN, Simsek E, et al. A novel thyroid hormone receptor-beta mutation that fails to bind nuclear receptor corepressor in a patient as an apparent cause of severe, predominantly pituitary resistance to thyroid hormone. J Clin Endocrinol Metab. 2006;91(5):1887–95.
56. 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 Endocr. 1967;27:279–94.
57. Takeda T, Sakurai A, DeGroot LJ, Refetoff S. Recessive inheritance of thyroid hormone resistance caused by complete deletion of the protein-coding region of the thyroid hormone receptor-β gene. J Clin Endocrinol Metab. 1992;74:49–55.
58. Barkoff MS, Kocherginsky M, Anselmo J, Weiss RE, Refetoff S. Autoimmunity in patients with resistance to thyroid hormone. J Clin Endocrinol Metab. 2010;95(7):3189–93.
59. Brucker-Davis F, Skarulis MC, Grace MB, et al. Genetic and clinical features of 42 kindreds with resistance to thyroid hormone: The National Institutes of Health prospective study. Ann Intern Med. 1995;123: 572–83.
60. Weiss RE, Refetoff SE. Effect of thyroid hormone on growth: lessons from the syndrome of resistance to thyroid hormone. Endocrinol Metab Clin North Am. 1996;25:719–30.
61. Mitchell CS, Savage DB, Dufour S, et al. Resistance to thyroid hormone is associated with raised energy expenditure, muscle mitochondrial uncoupling, and hyperphagia. J Clin Invest. 2010;120(4): 1345–54.
62. Matochik JA, Zametkin AJ, Cohen RM, Hauser P, Weintraub BD. Abnormalities in sustained attention and anterior cingulate gyrus metabolism in subjects with resistance to thyroid hormone. Brain Res. 1996;723:23–8.
63. Weiss RE, Stein MA, Refetoff S. Behavioral effects of liothyronine (L-T3) in children with Attention Deficit Hyperactivity Disorder in the presence and absence of resistance to thyroid hormone. Thyroid. 1997;7: 389–93.
64. Stein MA, Weiss RE, Refetoff S. Neurocognitive characteristics of individuals with resistance to thyroid hormone: comparisons with individuals with attention-deficit hyperactivity disorder. J Dev Behav Pediatr. 1995;16:406–11.
65. Kahn BB, Weintraub BD, Csako G, Zweig MH. Facticious elevation of thyrotropin in a new ultrasensitive assay: implications for the use of monoclonal antibodies in "sandwich" immunoassay. J Clin Endocrinol Metab. 1988;66:526–33.
66. Burrow GN, Fisher DA, Larsen PR. Maternal and fetal thyroid function. N Engl J Med. 1994;331: 1072–8.
67. Huang MJ, Liaw YF. Clinical associations between thyroid and liver diseases. J Gastroenterol Hepatol. 1995;10:344–50.
68. Pannain S, Feldman M, Eiholzer U, Weiss RE, Scherberg NH, Refetoff S. Familial dysalbuminemic hyperthyroxinemia in a Swiss family caused by a mutant albumin (R218P) shows an apparent discrepancy between serum concentration and affinity for thyroxine. J Clin Endocrinol Metab. 2000;85: 2786–92.
69. Petersen CE, Ha CE, Jameson DM, Bhagavan NV. Mutations in a specific human serum albumin thyroxine binding site define the structural basis of familial dysalbuminemic hyperthyroxinemia. J Biol Chem. 1996;271:19110–7.
70. Martino E, Bartalena L, Bogazzi F, Braverman LE. The effects of amiodarone on the thyroid. Endocr Rev. 2001;22:240–54.
71. Roca RP, Blackman MR, Ackerley MB, Harman SM, Gregerman RI. Thyroid hormone elevations during acute psychiatric illness: relationship to severity and distinction from hyperthyroidism. Endocr Res. 1990;16:415–47.

72. Beck-Peccoz P, Bruckner-Davis F, Persani L, Smallridge RC, Weintraub BD. Thyrotropin-secreting pituitary tumors. Endocr Rev. 1996;17: 610–38.
73. Safer JD, Colan SD, Fraser LM, Wondisford FE. A pituitary tumor in a patient with thyroid hormone resistance: a diagnostic dilemma. Thyroid. 2001;11: 281–91.
74. Bogazzi F, Manetti L, Tomisti L, et al. Thyroid color flow Doppler sonography: an adjunctive tool for differentiating patients with inappropriate thyrotropin (TSH) secretion due to TSH-secreting pituitary adenoma or resistance to thyroid hormone. Thyroid. 2006;16(10):989–95.
75. Wu SY, Sadow PM, Refetoff S, Weiss RE. Tissue responses to thyroid hormone in a kindred with resistance to thyroid hormone harboring a commonly occurring mutation in the thyroid hormone receptor beta gene (P453T). J Lab Clin Med. 2005;146(2): 85–94.
76. Asteria C, Rajanayagam O, Collingwood TN, et al. Prenatal diagnosis of thyroid hormone resistance. J Clin Endocrinol Metab. 1999;84:405–10.
77. Takeda T, Suzuki S, Liu RT, Degroot LJ. Triiodothyroacetic acid has unique potential for therapy of resistance to thyroid hormone. J Clin Endocrinol Metab. 1995;80:2033–40.
78. Torre P, Bertoli M, Di Giovanni S, et al. Endocrine and neuropsychological assessment in a child with a novel mutation of thyroid hormone receptor: response to 12-month triiodothyroacetic acid (TRIAC) therapy. J Endocrinol Invest. 2005;28(7): 657–62.
79. Hamon B, Hamon P, Bovier-Lapierre M, et al. A child with resistance to thyroid hormone without thyroid hormone receptor gene mutation: a 20-year follow-up. Thyroid. 2008;18(1):35–44.
80. Guran T, Turan S, Bircan R, Bereket A. 9 years follow-up of a patient with pituitary form of resistance to thyroid hormones (PRTH): comparison of two treatment periods of D-thyroxine and triiodothyroacetic acid (TRIAC). J Pediatr Endocrinol Metab. 2009;22(10):971–8.
81. Hashimoto A, Shi Y, Drake K, Koh JT. Design and synthesis of complementing ligands for mutant thyroid hormone receptor TRbeta(R320H): a tailor-made approach toward the treatment of resistance to thyroid hormone. Bioorg Med Chem. 2005;13(11):3627–39.
82. Weiss RE, Dumitrescu A, Refetoff S. Approach to the patient with resistance to thyroid hormone and pregnancy. J Clin Endocrinol Metab. 2010;95(7): 3094–102.
83. Anselmo J, Cao D, Karrison T, Weiss RE, Refetoff S. Fetal loss associated with excess thyroid hormone exposure. JAMA. 2004;292(6):691–5.
84. Jansen J, Friesema EC, Milici C, Visser TJ. Thyroid hormone transporters in health and disease. Thyroid. 2005;15(8):757–68.
85. Friesema EC, Grueters A, Biebermann H, et al. Association between mutations in a thyroid hormone transporter and severe X-linked psychomotor retardation. Lancet. 2004;364(9443):1435–7.
86. Dumitrescu AM, Liao XH, Best TB, Brockmann K, Refetoff S. A novel syndrome combining thyroid and neurological abnormalities is associated with mutations in a monocarboxylate transporter gene. Am J Hum Genet. 2004;74(1):168–75.
87. Dumitrescu AM, Liao XH, Weiss RE, Millen K, Refetoff S. Tissue-specific thyroid hormone deprivation and excess in monocarboxylate transporter (mct) 8-deficient mice. Endocrinology. 2006;147(9):4036–43.
88. Di Cosmo C, Liao XH, Dumitrescu AM, Weiss RE, Refetoff S. A thyroid hormone analog with reduced dependence on the monocarboxylate transporter 8 for tissue transport. Endocrinology. 2009;150(9):4450–8.
89. Dumitrescu AM, Liao XH, Abdullah MS, et al. Mutations in SECISBP2 result in abnormal thyroid hormone metabolism. Nat Genet. 2005;37(11): 1247–52.
90. Di Cosmo C, McLellan N, Liao XH, et al. Clinical and molecular characterization of a novel selenocysteine insertion sequence-binding protein 2 (SBP2) gene mutation (R128X). J Clin Endocrinol Metab. 2009;94(10):4003–9.
91. Schoenmakers E, Agostini M, Mitchell C, et al. Mutations in the selenocysteine insertion sequence-binding protein 2 gene lead to a multisystem selenoprotein deficiency disorder in humans. J Clin Invest; 2010;120(12):4220–35.
92. Cohen RN, Weintraub BD, Wondisford FE. Chemistry and biosynthesis of thyrotropin. In: Braverman LE, Utiger RD, editors. Werner and Ingbar's the thyroid. 8th ed. Philadelphia, PA: Lippincott, Williams, and Wilkins; 2005. p. 159–75.
93. Stanbury JB, Rocmans P, Buhler UK, Ochi Y. Congenital hypothyroidism with impaired thyroid response to thyrotropin. N Engl J Med. 1968;279: 1132–6.
94. Sunthornthepvarakul T, Gottschalk ME, Hayashi Y, Refetoff S. Brief report: resistance to thyrotropin caused by mutations in the thyrotropin-receptor gene. N Engl J Med. 1995;332:155–60.
95. Rapoport B, Chazenbalk GD, Jaume JC, McLachlan SM. The thyrotropin (TSH) receptor: interaction with TSH and autoantibdies. Endocr Rev. 1998;19:673–716.
96. Zhang M, Tong KPT, Fremont V, et al. The extracellular domain suppresses constitutive activity of the transmembrane domain of the human TSH receptor: implications for hormone-receptor interaction and antagonist design. Endocrinology. 2000;141: 3514–7.
97. Libert F, Passage E, Lefort A, Vassart G, Mattei MG. Localization of human thyrotropin receptor gene to chromosome region 14q31 by in situ hybridization. Cytogenet Cell Genet. 1990;54:82–3.
98. Rousseau-Merck MF, Misrahi M, Loosfelt H, Atger M, Milgrom E, Berger R. Assignment of the human thyroid stimulating hormone receptor (TSHR) gene to chromosome 14q31. Genomics. 1990;8:233–6.
99. de Roux N, Misrahi M, Brauner R, et al. Four families with loss of function mutations of the

thyrotropin receptor. J Clin Endocrinol Metab. 1996;81:4229–35.
100. Clifton-Bligh RJ, Gregory JW, Ludgate M, et al. Two novel mutations in the thyrotropin (TSH) receptor gene in a child with resistance to TSH. J Clin Endocrinol Metab. 1997;82:1094–100.
101. Russo D, Betterle B, Arturi F, Chiefari E, Girelli ME, Filetti S. A novel mutation in the thyrotropin (TSH) receptor gene causing loss of TSH binding but constitutive receptor activation in a family with resistance to TSH. J Clin Endocrinol Metab. 2000;85:4238–42.
102. Abramowicz MJ, Duprez L, Parma J, Vassart G, Heinrichs C. Familial congenital hypothyroidism due to inactivating mutation of the thyrotropin receptor causing profound hypoplasia of the thyroid gland. J Clin Invest. 1997;99:3018–24.
103. Biberman H, Schoneberg T, Krude H, Schultz G, Guderman T, Gruters A. Mutations of the human thyrotropin receptor gene causing thyroid hypoplasia and persistent congenital hypothyroidism. J Clin Endocrinol. 1997;82:3471–80.
104. Gagne N, Parma J, Deal C, Vassart G, Van Vliet G. Apparent congenital athyreosis contrasting with normal plasma thyroglobulin levels and associated with inactivating mutations in the thyrotropin receptor gene: are athyreosis and ectopic thyroid distinct entities? J Clin Endocrinol Metab. 1998;83:1771–5.
105. Tonacchera M, Agretti P, Pinchera A, et al. Congenital hypothyroidism with impaired thyroid response to thyrotropin (TSH) and absent circulating thyroglobulin: evidence for a new inactivating mutation of the TSH receptor gene. J Clin Endocrinol Metab. 2000;85:1001–8.
106. Xie J, Pannain S, Pohlenz J, et al. Resistance to thyrotropin (TSH) in three families is not associated with mutations in the TSH receptor or TSH. J Clin Endocrinol. 1997;82:3933–40.
107. Weinstein LS, Liu J, Sakamoto A, Xie T, Chen M. Minireview: GNAS: normal and abnormal functions. Endocrinology. 2004;145(12):5459–64.
108. Grasberger H, Ringkananont U, Lefrancois P, Abramowicz M, Vassart G, Refetoff S. Thyroid transcription factor 1 rescues PAX8/p300 synergism impaired by a natural PAX8 paired domain mutation with dominant negative activity. Mol Endocrinol. 2005;19(7):1779–91.
109. Nagasaki K, Narumi S, Asami T, Kikuchi T, Hasegawa T, Uchiyama M. Mutation of a gene for thyroid transcription factor-1 (TITF1) in a patient with clinical features of resistance to thyrotropin. Endocr J. 2008;55(5):875–8.
110. Grasberger H, Mimouni-Bloch A, Vantyghem MC, et al. Autosomal dominant resistance to thyrotropin as a distinct entity in five multigenerational kindreds: clinical characterization and exclusion of candidate loci. J Clin Endocrinol Metab. 2005;90(7):4025–34.
111. Narumi S, Muroya K, Abe Y, et al. TSHR mutations as a cause of congenital hypothyroidism in Japan: a population-based genetic epidemiology study. J Clin Endocrinol Metab. 2009;94(4):1317–23.
112. Bochukova E, Schoenmakers N, Agostini M, et al. A mutation in the thyroid hormone receptor alpha gene. N Engl J Med. 2012;366:243-9.