

Resistance to Thyroid Hormone (RTH) in the Absence of Abnormal Thyroid Hormone Receptor (TR) (nonTR-RTH)

Roy E. Weiss and Samuel Refetoff

Departments of Medicine and Pediatrics, University of Chicago, Chicago, IL, USA

Invited by: Sheue-yann Cheng; Reviewing Editor: Luca Persani

Conflict of interest declaration: None

Correspondence to:

Roy E. Weiss, MD, PhD

Section of Adult and Pediatric Endocrinology, Diabetes and Metabolism

The University of Chicago, MC 3090

5841 S. Maryland Ave

Chicago, IL 60637

TEL: 773-702-9266

FAX: 773-834-3966

email: rweiss@medicine.bsd.uchicago.edu

ABSTRACT

Resistance to thyroid hormone (RTH) is an inherited syndrome of reduced end-organ responsiveness to thyroid hormone (TH). It is characterized by elevated TH levels and nonsuppressed serum TSH in the presence of a goiter. As the term implies, subjects with RTH have impaired responsiveness to TH manifested to variable degrees in different tissues. TH action is mediated by the TH receptors (TR) β and α . The etiology of RTH is usually due to a mutation in the *TR β* gene. The mutant TR β proteins have impaired TH binding and/or cause impaired activation of TH-responsive genes. However, 15% of subjects with a clinically identical RTH phenotype have no demonstrable mutations in the *TR β* gene or in *TR α* gene, when examined. These subjects are classified as nonTR-RTH. The lack of *TR* gene mutation has been confirmed by sequencing both cDNA and gDNA and, in 4 families, *TR β* mutations have additionally been excluded by linkage analysis. We have identified 39 affected individuals belonging to 29 kindreds with nonTR-RTH. This relatively large number of individuals has allowed us to appreciate subtle differences in the demographics of nonTR-RTH compared to RTH with *TR β* mutations, including a female preponderance in the former (2.5:1). However, the key component to the phenotypes, namely TH and TSH levels, do not differ from RTH caused by *TR β* gene mutations. Despite the discovery of nonTR-RTH 15 years ago, the molecular basis for this condition has remained elusive.

Key-words: nonTR-RTH; thyroid hormone receptor β ; thyroid hormone receptor α ; goiter; TSH

TH Action and Reduced Sensitivity to the Hormone

TH action requires more than 30 different cofactors which involve several distinct processes. The first step in TH action is for the hormone to enter the cell. This is achieved through active cell membrane transport. T_4 and T_3 transport is mediated by an active transport process through a family of TH transporters, including the monocarboxylate transporter 8 (MCT-8) (1). In the cell T_4 is either activated by 5' deiodination to form T_3 or inactivated by 5-deiodination to form reverse T_3 . One mode of TH action is through rapid, non-genomic pathways, which are exerted at the level of the plasma membrane and cytoplasm (2). However, the principal, best-studied and characterized effect requires the translocation of the hormone into the nucleus where it interacts with TRs to activate or repress transcription of specific target genes. These genes contain nucleotide sequences at or near their promoter regions (TH response elements or TREs) recognized by TRs for binding. In the absence of TH, TRs homodimerize and associate with nuclear corepressors. These complexes have silencing effect on genes positively regulated by TH. T_3 binding to TRs produces conformational changes, which trigger a chain of processes, including release of the corepressor, often heterodimerization of TR with the retinoid X receptor (RXR) and recruitment of coactivators and a large number of other proteins. In positively controlled genes by TH, this results in making the DNA more accessible for transcription (3). If any of the above molecules (transporters, TH activating enzymes, repressors, activators, etc.) were dysfunctional, a form of reduced TH sensitivity could ensue some sharing the phenotype of RTH. However, since some of the accessory molecules serve in more than one pathway, the phenotype resulting from a defect cannot be predicted.

Clinical Features of RTH and Course of the Disease

The cardinal features of RTH are: 1) elevated serum levels of free T_4 and often free T_3 ; 2) normal or slightly increased serum thyrotropin (TSH); and 3) absence of typical symptoms and metabolic consequences of TH excess (4, 5).

The precise incidence of RTH is not known as it is usually not detected by routine neonatal screening for hypothyroidism, using blood spot TSH determination. A limited screen for high T_4 values found a prevalence of 1:40,000 live births (6).

Characteristic of the RTH syndrome is the paucity of specific clinical manifestations. When present, they are variable from one patient to another (4, 7) Presenting symptoms and signs are goiter, hyperactive behavior, learning disabilities, developmental delay and sinus tachycardia. The finding of elevated serum TH levels in association with nonsuppressed TSH usually leads to suspect the diagnosis.

The majority of subjects maintain a normal metabolic state at the expense of high TH levels. This compensation for the hyposensitivity to TH is variable not only among individuals but also in different tissues. As a consequence, clinical and laboratory evidence of TH deficiency and excess often coexist. For example, delayed growth and bone maturation and learning disabilities, suggestive

of hypothyroidism, can be present along with hyperactivity and tachycardia, compatible with thyrotoxicosis. Common clinical features are given in Table 1. They occur with similar frequency in subject with *TRβ* gene mutations or without. Frank symptoms of hypothyroidism are more common in individuals who have received treatment to normalize their circulating TH levels.

Table 1. Clinical Features: Frequency of Symptoms and Signs

FINDINGS		TR-RTH FREQUENCY*	NonTR-RTH FREQUENCY**
Thyroid gland	Goiter	66-95	83
Heart	Tachycardia	33-75	58
Nervous system	Emotional disturbances	60	50
	Hyperkinetic behavior	33-68	60
	Attention deficit hyperactivity disorder	40-60	75
	Learning disability	30	50
	Mental retardation (IQ <70)	4-16	***
	Hearing loss (sensorineural)	10-22	5
Growth and development	Short stature (<5%)	18-25	N/A
	Delayed bone age >2 SD	29-47	N/A
	Low body mass index (in children)	33	N/A
Recurrent ear and throat infections		55	12
Autoimmune thyroid disease		23	14

IQ = intellectual quotient

*Data derived from (4,7,8)

N/A insufficient data available

**NonTR-RTH associated with: hypertension (2); obesity (4); atrial fibrillation (2); pectus excavatum (2)

***IQ testing is only available on 7 subjects, of these 4 had IQ <70

Goiter is by far the most common finding, reported in 66-95% of cases. Enlargement is usually diffuse. Sinus tachycardia is also very common, which, together with goiter, often lead to the erroneous diagnosis of autoimmune thyrotoxicosis.

About one-half of subjects with RTH have some degree of learning disability with or without attention deficit hyperactivity disorder (4). One-quarter have intellectual quotients (IQ) less than 85 but frank mental retardation (IQ <60) was found only in 3% of cases. Deaf-mutism and color blindness occurred in all three affected members of a single family with *TRβ* gene deletion (8).

The course of the disease is as variable as its presentation. Most subjects have normal growth and development, and lead a normal life at the expense of high TH levels and a small goiter. Others present variable degrees of mental and growth retardation. Symptoms of hyperactivity tend to improve with age. Goiter usually recurs after surgery. As a consequence, some subjects have been submitted to several thyroidectomies or treatments with radioiodide (4).

RTH and *TRβ* Gene Mutations

In the majority of cases, RTH is caused by mutations in the *TRβ* gene, located on chromosome 3. Mutations are found in the carboxyl terminus covering the ligand-binding domain and adjacent hinge domain of the *TRβ* protein (9-11). They are contained within three clusters rich in CG "hot spots", separated by areas devoid of mutations (cold regions). The latter are located between codons 282 and 310, and with the exception of 383, codons 353 and 429. No mutation has been reported upstream of codon 234. As cold regions are not devoid of "hot spots", the lack of mutations reflects the observation that mutations in the second cold region does not impair TR function and, therefore, is not expected to produce a phenotype (5)

TRβ gene defects have been identified in 473 families comprising more than 150 distinct mutations. The authors have found mutations in 148 families and a partial listing is available from <http://www.receptors.org/cgi-bin/nrmd/nrmd.py>. Though mostly missense, nucleotide deletion and insertions producing frameshifts have created nonsense proteins with two additional aminoacids or produced truncated receptors. In only one family complete *TRβ* gene deletion resulted in recessively inherited RTH. The mutant *TRβ* molecules have either reduced affinity for T₃ (9, 10) or impaired interaction with one of the cofactors involved in the mediation of thyroid hormone action (10, 12-14). As TR mutants are still able to bind to TREs on DNA and dimerize with normal TRs or the RXR partner, they interfere with the function of the normal TRs, explaining the dominant mode of inheritance. Therefore, it is not surprising that in the single family reported with a deletion of all coding sequences of the *TRβ* gene, only homozygotes manifest the phenotype of RTH (8).

No mutations in the *TRα* gene have been identified so far in humans. Based on observations in transgenic mice a putative *TRα* gene mutation should not cause typical thyroid function tests as seen in RTH.

nonTR-RTH: Definition and Demographics

In 1996, we reported a family in which RTH manifested in the absence of *TRβ* gene mutation and a *TRβ* gene transcripts of normal size and abundance (15). In addition abnormalities of TRβ were excluded in this family because of absence of phenotype cosegregation with the *TRβ* allele. Nevertheless, fibroblasts were resistant to the *in-vitro* effect of TH. Recombinant wild-type (WT) TRβ interacted aberrantly with nuclear extracts of fibroblasts from affected individuals of the family but not from normal individuals or subjects with complete *TRβ* gene deletion and Far Western analysis revealed an additional 84 kD band. More families with nonTR-RTH were subsequently reported (16-19).

We evaluated 39 affected subjects with nonTR-RTH and 139 unaffected first degree relatives from 29 different families. Comparison of the thyroid function test results of the 39 affected by nonTR-RTH with the corresponding 473 subjects with *TRβ* gene mutations showed no differences (Table 2). While RTH caused by *TRβ* gene mutations has equal gender incidence, nonTR-RTH is more common in females (2.5:1). The possibility of an autoimmune component was excluded by the absence of higher frequency of thyroid autoantibodies. NonTR-RTH occurred mostly sporadically with only 6 families having more than one affected subject. Recessive inheritance and mosaicism need to be considered and when possible excluded.

Laboratory Diagnosis of nonTR-RTH

The laboratory diagnosis of nonTR-RTH is similar to that previously published for RTH. No single test is conclusive and diagnosis of RTH must rest on a combination of test and observations: 1) the absence of an elevated serum concentration of the alpha pituitary glycoprotein subunit; 2) stimulation of TSH following the administration of TSH-releasing hormone (TRH); 3) absence of elevated serum sex hormone-binding globulin concentration (SHBG), reflecting a euthyroid state; and 4) ability to suppress serum TSH with supraphysiological doses of L-T₃.

The measurement of responses to the administration of incremental doses of TH is the best mean to assess the presence and magnitude of the hormonal resistance and obtain a clinical diagnosis of RTH. The rationale for the use of L-T₃ rather than L-T₄ is its direct effect on tissues, independent of variations in T₄ metabolism. The rapid onset of L-T₃ action reduces the period of hormone administration and the shorter half-life of this hormone decreases the duration of symptoms that may arise in hormonally responsive subjects. It involves the administration of three incremental doses of L-T₃, each for the duration of 3 days. Amounts range from just below to 3-times above replacement. Hospitalization for 11 days is required for the detailed study, which includes measurement of sleeping pulse, basal metabolic rate (BMR) and calorie balance for which food intake is controlled and urinary nitrogen excretion is measured (4). A TRH test is performed at baseline and at the time of the administration of the last L-T₃ dose of each increment. Blood samples drawn over

the period of 180 min are used to measure the TSH and prolactin responses as well as the nadir and peak of serum T_3 achieved with each incremental dose. Measurements of TG and T_4 assess the magnitude of thyroid gland suppression, while those of serum cholesterol, creatine kinase, ferritin, SHBG and osteocalcin (OC), the responses of peripheral tissues to the hormone. Whereas these tests can confirm or exclude RTH, they are unable to distinguish TR β -RTH from nonTR-RTH (Figure 1).

Differential Diagnosis of nonTR-RTH

The combination of non-suppressed (normal or slightly elevated) serum TSH with increased concentrations of T_4 , T_3 or both, is characteristic of the three syndromes of reduced sensitivity to TH. However, the most difficult differential diagnosis to make is between RTH due to *TR β* gene mutations and nonTR-RTH as appreciated from the overlapping phenotype and clinical characteristics. Gene sequencing of both cDNA and gDNA and ideally linkage data (when family size permits) can be very helpful to distinguish the two. In addition genetic analysis using several tissue as source of DNA can identify subject with mosaicism due to de-novo mutation.

1. MCT8 Mutation (Transport Defect)

Although the clinical presentation of TH cell transporter defects involving other cell-membrane transporters than MCT8, is unknown, the latter always presents in males accompanied by psychomotor abnormalities, including truncal hypotonia, limb spasticity, poor head control, dyskinetic movements and absent or garbled speech. However, presence of the characteristic thyroid test abnormalities is mandatory. Typical serum test abnormalities are high T_3 , low reverse T_3 and often slightly reduced T_4 concentrations.

The lowish serum T_4 concentration and psychomotor abnormalities should enable the physician to distinguish MCT8 from RTH (20). Sequencing of the *MCT8* gene in subjects with similar psychomotor manifestations but no characteristic thyroid test changes have yielded negative results (21).

2. SECISBP-2 Mutation (T_4 to T_3 Conversion Defect)

Elevated serum T_4 can be observed in subjects with defects in the conversion of T_4 to T_3 . Patients with defects in 5' deiodination are unable to generate sufficient amount of T_3 resulting in pituitary stimulation of TSH and increase in serum T_4 concentration. To date the only gene mutation

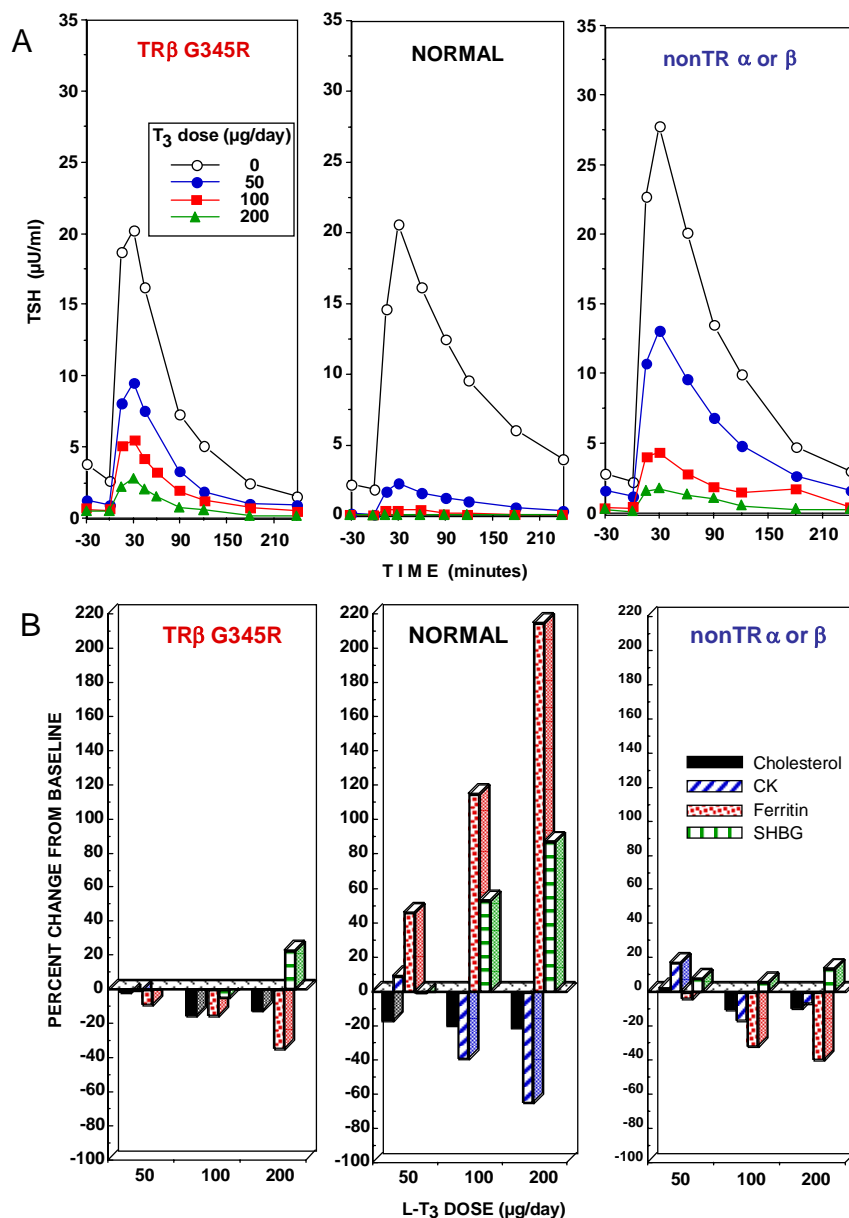


Figure 1. A. Thyrotroph responses to TRH stimulation at baseline and after the administration of graded doses of L-T₃. The hormone was given in three incremental doses, each for 3 days. Results are shown for patients with RTH in the presence (left) or absence (right) of a TRβ gene mutation, together with the unaffected mother of the patient with nonTR-RTH (center). B. Responses of peripheral tissues to the administration of L-T₃ in the presence or absence of mutations in the TRβ gene. Note the stimulation of ferritin and sex hormone binding globulin (SHBG) and the suppression of cholesterol and creatine kinase (CK) in the normal subject. Responses in affected subjects, with or without a TRβ gene mutation, were blunted or paradoxical. [Modified from www.thyroidmanager.org, chapter 16c].

found to result in a iodothyronine deiodinase defect is selenocysteine incorporation sequence-binding protein 2 (SECISBP-2). The defect causes a selective, though generalized reduction in the synthesis of selenoproteins. These subjects are easily distinguished from RTH subjects due to the low T₃ (22). Growth retardation in childhood and azoospermia in adulthood are common.

3. Binding Defects (TBG Excess; FDH)

RTH is characterized by elevation of usually both free T₄ and T₃ levels with non suppressed TSH. Subjects with familial dysalbuminemic hyperthyroxinemia caused by albumin gene mutations, or thyroxine binding globulin (TBG) excess present with elevated total T₄ and T₃, but the free hormone concentrations, when measured by equilibrium dialysis or ultrafiltration, are normal.

4. Mosaicism

Any subject expressing the RTH phenotype in whom no mutation can be demonstrated in a particular cell lineage may have mosaicism. If peripheral blood leukocytes (the most common source of DNA) are not found to harbor a *TRβ* gene mutation, DNA from skin fibroblasts, buccal epithelial cells, sperm (all easily accessible) or other available tissues should be analyzed (23). Such a patient was initially believed to have nonTR-RTH. In the list of subjects with nonTR-RTH (Table 2), the number of tissues examined are listed.

5. TSH Secreting Pituitary Tumor

Patients with TSH secreting tumors display thyroid function tests similar to those of subjects with nonTR-RTH and also have no detectable *TRβ* gene mutations. Pituitary microadenoma may be too small to be detected by imaging. More often a positive MRI may be associated with RTH. The finding of elevated serum α-subunit to TSH ratios and failure to respond to TSH releasing hormone (TRH) are useful tests to distinguish TSH secreting pituitary tumors from RTH, irrespective of the presence or absence of *TRβ* gene mutation. Furthermore, the presence of more than one family member with the same phenotype makes a TSH pituitary tumor unlikely. Rarely, somatic *TRβ* gene mutations can produce TSH secreting adenomas (24).

Treatment of nonTR-RTH

As treatment of RTH is not dictated by the presence and nature of the *TRβ* gene mutation, the therapeutic approach in nonTR-RTH is not different, being aimed at alleviating symptoms when present. Stigmata of TH deficiency are treated with L-T₄ and symptoms of TH excess are treated with β adrenergic blockers. It is important not to treat asymptomatic, fully compensated, individuals with the sole purpose of correcting the laboratory test abnormalities. Prior ablative treatment, resulting from misdiagnosis, requires the judicious administration of TH, often in supraphysiological doses.

Table 2. Genetic studies thyroid function tests and demographics of families with nonTR-RTH

Family ID	#Affected	#Normal*	Linkage to TR β	FT ₄ ** %ULN	FT ₃ ** %ULN	TSH** mU/L	n. of tissues	Ethnic origin	Country
Mm***	3	10	Excl	259	218	17.4	2	Norwegian/Irish/German	USA
Mal	3	21	Excl	189	222	2.1	2	Irish/Scottish/German	USA
Muna***	5	10	not Excl	131	98	5.9	1	Turkish	Turkey
Mpa**	2	2	nonInf	103	109	7.2	1	European	USA
Mlv**	2	3		147	92	4.2	2	Austrian/German (non Jewish)	Israel
Magc	2	7	nonInf	137	119	3.5	3	Turkish	Turkey
Mbz	1	2		114	124	5.5	1	Turkish	Turkey
Msn	1	9	Excl	193	183	3.0	1	German/Duch/Amerindian	USA
Mch	1	8	Excl	174	142	1.9	2	South Chinese (Han)	Hong Kong
Mgd***	1	3		170	84	15.3	1	Dutch/French/German	USA
Mli	1	2		154	137	3.3	1	European	USA
Mk	1	10		199	169	2.1	2	Ashkenazic/Russian/German	USA
Mry	1	0		142	117	3.1	1	European	USA
Msh	1	7		170	192	7.0	3	European	USA
Mby	1	4		190-	121	1.8	2	Irish	Ireland
Maf	1	3		211	144	1.0	1	Hispanic	USA
Mcap	1	1		177	209	4.1	1	European	USA
Mdig	1	2		124	121	1.9	1	Syrian/Irish/Scottish/Polish	USA
Mmg	1	3		180	172	4.7	1	European	USA
Mpe	1	2		117	139	7.6	2	Italian	USA
Mve***	1	6		142	70	143	1	Chilean (Hispanic)	Italy
Meg	1	6		145	156	5.1	2	European	USA
Mwm	1	5		135	110	6.1	1	African American	USA
Mdeb	1	4		253	185	2.6	1	French	France
Mkam	1	0		144	101	9.4	1	Asian Indian	USA
Mdor	1	0		143	112	1.8	1	Unknown	USA
Msz	1	5		174	154	5.2	1	Polish	USA
Mno	1	3		147	132	2.2	1	European	USA
Mer	1	2		154	114	4.3	2	Turkish	Turkey
Total	39	139		176±58	153±64	4.4±4.0			
RTH with TRβ mutations	473	803		189±43	188±45	3.6±3.5			

ULN = Upper Limit of Normal; † 1 = circulating white blood cells (WBC); 2 = WBC and fibroblast; 3 = an additional tissue.

* Including relatives by marriage.

** For more than one affected family member, average value is given.

*** Patients on antithyroid drugs or after thyroidectomy are not included in the calculation of the overall mean.

Excl = excluded by linkage analysis; **nonInf** = non informative.

References

1. Heuer H, Visser TJ: Minireview: Pathophysiological importance of thyroid hormone transporters. *Endocrinology* 150:1078-1083, 2009.
2. Bassett JH, Harvey CB, Williams GR: Mechanisms of thyroid hormone receptor-specific nuclear and extra nuclear actions. *Mol Cell Endocrinol* 213:1-11, 2003.
3. Fondell JD, Ge H, Roeder RG: Ligand induction of a transcriptionally active thyroid hormone receptor coactivator complex. *Proc Natl Acad Sci U S A* 93:8329-8333, 1996.
4. Refetoff S, Weiss RE, Usala SJ: The syndromes of resistance to thyroid hormone. *Endocr Rev* 14:348-399, 1993.
5. Hayashi Y, Sunthornthepvarakul T, Refetoff S: Mutations of CpG dinucleotides located in the triiodothyronine (T₃)-binding domain of the thyroid hormone receptor (TR) beta gene that appears to be devoid of natural mutations may not be detected because they are unlikely to produce the clinical phenotype of resistance to thyroid hormone. *J Clin Invest* 94:607-615, 1994.
6. 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* 143:296-301, 2003.

7. Beck-Peccoz P, Chatterjee VK: The variable clinical phenotype in thyroid hormone resistance syndrome. *Thyroid* 4:225-232, 1994.
8. Takeda K, 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-beta gene. *J Clin Endocrinol Metab* 74:49-55, 1992.
9. Adams M, Matthews C, Collingwood TN, Tone Y, Beck-Peccoz P, Chatterjee KK: Genetic analysis of 29 kindreds with generalized and pituitary resistance to thyroid hormone. Identification of thirteen novel mutations in the thyroid hormone receptor beta gene. *J Clin Invest* 94:506-515, 1994.
10. Collingwood TN, Wagner R, Matthews CH, Clifton-Bligh RJ, Gurnell M, Rajanayagam O, Agostini M, Fletterick RJ, Beck-Peccoz P, Reinhardt W, Binder G, Ranke MB, Hermus A, Hesch RD, Lazarus J, Newrick P, Parfitt V, Raggatt P, de Zegher F, Chatterjee VK: A role for helix 3 of the TRbeta ligand-binding domain in coactivator recruitment identified by characterization of a third cluster of mutations in resistance to thyroid hormone. *Embo J* 17:4760-4770, 1998.
11. Weiss RE, Weinberg M, Refetoff S: Identical mutations in unrelated families with generalized resistance to thyroid hormone occur in cytosine-guanine-rich areas of the thyroid hormone receptor beta gene. Analysis of 15 families. *J Clin Invest* 91:2408-2415, 1993.
12. Liu Y, Takeshita A, Misiti S, Chin WW, Yen PM: Lack of coactivator interaction can be a mechanism for dominant negative activity by mutant thyroid hormone receptors. *Endocrinology* 139:4197-4204, 1998.
13. 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* 273:30175-30182, 1998.
14. Yoh SM, Chatterjee VKK, Privalsky ML: Thyroid hormone resistance syndrome manifests as an aberrant interaction between mutant T₃ receptor and transcriptional corepressor. *Mol Endocrinol* 11:470-480, 1997.
15. Weiss RE, Hayashi Y, Nagaya T, Petty KJ, Murata Y, Tunca H, Seo H, Refetoff S: Dominant inheritance of resistance to thyroid hormone not linked to defects in the thyroid hormone receptor alpha or beta genes may be due to a defective cofactor. *J Clin Endocrinol Metab* 81:4196-4203, 1996.
16. Bottcher Y, Paufler T, Stehr T, Bertschat FL, Paschke R, Koch CA: Thyroid hormone resistance without mutations in thyroid hormone receptor beta. *Med Sci Monit* 13:CS67-70, 2007.
17. McDermott JH, Agha A, McMahon M, Gasparro D, Moeller L, Dumitrescu AM, Refetoff S, Sreenan S: A case of Resistance to Thyroid Hormone without mutation in the thyroid hormone receptor beta. *Ir J Med Sci* 174:60-64, 2005.
18. Pohlenz J, Weiss RE, Macchia PE, Pannain S, Lau IT, Ho H, Refetoff S: Five new families with resistance to thyroid hormone not caused by mutations in the thyroid hormone receptor beta gene. *J Clin Endocrinol Metab* 84:3919-3928, 1999.
19. Vlaeminck-Guillem V, Margotat A, Torresani J, D'Herbomez M, Decoulx M, Wemeau JL: Resistance to thyroid hormone in a family with no TRbeta gene anomaly: pathogenic hypotheses. *Ann Endocrinol (Paris)* 61:194-199, 2000.
20. Schwartz CE, May MM, Carpenter NJ, Rogers RC, Martin J, Bialer MG, Ward J, Sanabria J, Marsa S, Lewis JA, Echeverri R, Lubs HA, Voeller K, Simensen RJ, Stevenson RE: Allan-Herndon-Dudley syndrome and the monocarboxylate transporter 8 (MCT8) gene. *Am J Hum Genet* 77:41-53, 2005.
21. Frints SG, Lenzner S, Bauters M, Jensen LR, Van Esch H, des Portes V, Moog U, Macville MV, van Roozendaal K, Schrandt-Stumpel CT, Tzschach A, Marynen P, Fryns JP, Hamel B, van Bokhoven H, Chelly J, Beldjord C, Turner G, Gecz J, Moraine C, Raynaud M, Ropers HH, Froyen G, Kuss AW: MCT8 mutation analysis and identification of the first female with Allan-Herndon-Dudley syndrome due to loss of MCT8 expression. *Eur J Hum Genet* 16:1029-1037, 2008.

22. Dumitrescu AM, Liao XH, Abdullah MS, Lado-Abeal J, Majed FA, Moeller LC, Boran G, Schomburg L, Weiss RE, Refetoff S: Mutations in SECISBP2 result in abnormal thyroid hormone metabolism. *Nat Genet* 37:1247-1252, 2005.
23. Mamasiri S, Yesil S, Dumitrescu AM, Liao XH, Demir T, Weiss RE, Refetoff S: Mosaicism of a thyroid hormone receptor-beta gene mutation in resistance to thyroid hormone. *J Clin Endocrinol Metab* 91:3471-3477, 2006.
24. Ando S, Sarlis NJ, Oldfield EH, Yen PM: Somatic mutation of TRbeta can cause a defect in negative regulation of TSH in a TSH-secreting pituitary tumor. *J Clin Endocrinol Metab* 86:5572-5576, 2001.