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Pathogenic mechanism of mutations in the *thyroid hormone receptor β* gene

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ABSTRACT. ***Background:*** **Resistance to thyroid hormone (RTH) is characterized by a variable degree of reduced tissue sensitivity to thyroid hormone (TH). It is usually caused by mutations in the *TH receptor-β* (*TRβ*) gene.** ***Aims:*** **To characterize clinical and molecular features of a Thai patient with RTH. Functional significance of the identified mutation as well as other uncharacterized *TRβ* mutations was also investigated.** ***Materials and methods:*** **Exons 3-10 of the *TRβ* gene were assessed by PCR-sequencing. Functional characterization of the mutant *TRβ* was determined by the luciferase reporter system.** ***Results:*** **A mutation in exon 9 of the *TRβ* gene resulting in a methionine to threonine substitution at codon 313 was identified. The functional consequence of this mutation and other uncharacterized known mutations (p.I276L, p.I280S, p.L330S, p.G344A, p.M442T) was evaluated by transfection studies. Four out of 6 had a significant impairment of T_3-dependent transactivation. When co-transfected with the wild-type TRβ, all exhibited a dominant negative effect.** ***Conclusion:*** **A *de novo* mutation was identified in the patient with clinical diagnosis of RTH. Our findings provide a strong support that interfering with the T_3-mediated transcriptional activation of the wild-type TRβ independent of the ability to activate transcription is a major pathogenic mechanism causing RTH.**
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INTRODUCTION

Resistance to thyroid hormones (RTH) is an autosomal dominant inherited syndrome characterized by reduced tissue responsiveness to thyroid hormone (TH) resulting in elevated serum TH levels, normal or elevated serum TSH levels, and goiter. It is mostly caused by mutations in the *TH receptor (TR)-β* gene (1). The majority of the mutations have been identified in the T_3-binding domain and adjacent hinge region causing either a decreased T_3 binding activity or impaired interaction with cofactors involved in TH-mediated transcription (2, 3). It has been demonstrated that mutant TRβ have dominant negative activity by interfering with the function of the normal TR (4). Patients with RTH have clinical manifestations varying from clinical euthyroidism to thyrotoxicosis or hypothyroidism. In addition, different clinical features can be observed in members of the same family and individuals from different families with identical mutations. These phenotypic variability may be dependent on individual differences in the distribution of the TRβ in the tissues, the level of tissue expression of the mutant TRβ, effectiveness of compensatory mechanisms, or modifying genetic factors (5, 6).

We described a *de novo* mutation in a Thai patient with RTH who had a heterozygous missense mutation in exon 9 of the *TRβ* gene, resulting in a methionine (ATG) to threonine (ACG) substitution at codon 313 (p.M313T). We further explored functional properties of this mutation and compared it with 5 other uncharacterized known mutations by using the luciferase reporter gene assay (7-11). The underlying pathogenic mechanism was therefore elucidated.

Key-words: Dominant negative effect, mutations, resistance to thyroid hormone (RTH), thyroid hormone receptor-β.

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MATERIALS AND METHODS

Patient

The 5-yr-old proband was initially evaluated at a hospital for a persistent goiter since the age of 2 yr. She did not have clinical features of hyperactivity and thyrotoxicosis. She was healthy otherwise with appropriate developmental milestones. Thyroid function tests (TFT) revealed a free T_4 of 4.71 ng/dl (normal 0.8-1.8), a total T_3 of 376.5 ng/dl (normal 90-180 ng/dl) and TSH of 1.79 mU/ml (normal 0.3-4.1). She was initially given propylthiouracil (PTU) and later was treated with methimazole (MMI). The goiter became enlarged after the treatment with more increasing levels of TSH as shown in Table 1. When the patient was referred to us at the age of 7 yr, the medication was stopped. TFT after withdrawal of MMI for 2 months revealed an elevated free T_4 of 4.52 ng/dl and free T_3 of 12.03 pg/ml (normal 1.6-4.0) with unsuppressed TSH of 1.41 mU/ml. Thyroid enlargement decreased with the longest diameter reducing from 7 cm to 6.5 cm. Her parents and older sister had normal TFT. The pedigree of the family is showed in Figure 1.

Mutation analysis

After informed consent, genomic DNA was extracted from peripheral blood leukocytes of the proband and the parents using Qiagen DNA extraction kits according to manufacturer's in-

Table 1 - *Assessment of thyroid function in the proband.*

Age (yr)	Heart rate	Free T_4 (ng/dl)	Total T_3 (ng/dl)	TSH (mU/ml)	Therapy
5	110	4.71	376.5	1.79	PTU 5.9 mg/kg/day
5.2	100	4.81	342.6	3.06	PTU 8.3 mg/kg/day
5.3	90	4.57	321.1	4.96	PTU 10 mg/kg/day
5.5	90	3.75	347.9	4.70	MMI 0.6 mg/kg/day
5.6	100	2.61	380.1	23.37	MMI 0.9 mg/kg/day
5.8	80	1.41	333.1	78.02	MMI 0.9 mg/kg/day
5.11	90	0.197	123.7	>100	MMI 0.6 mg/kg/day
6	80	0.65	242.7	>100	-
6.1	100	6.92	-	2.48	MMI 0.5 mg/kg/day
6.5	90	3.37	-	24.21	MMI 0.5 mg/kg/day
6.10	90	1.32	373.3	>100	MMI 0.5 mg/kg/day

PTU: propylthiouracil; MMI: methimazole.

structions (Qiagen, Valencia, CA). Exons 3-10 of the *TRβ* gene were amplified by PCR using intronic primers (available upon request). PCR products were treated with ExoSAP-IT (USP Corporation, Cleveland, OH) according to the manufacturer's recommendations, and sent for direct sequencing (Macrogen Inc., Seoul, Korea). Sequence data were analyzed using Sequencher (version 4.2; Gene Codes Corporation, Ann Arbor, MI). The identified mutation was verified by two independent PCR reactions and sequencing using forward and reverse primers.

Construction of plasmids and site-directed mutagenesis

The expression vector pcDNAI/Amp-WT TR*β*1 and the reporter Palx3-Luc plasmid were kindly provided by Refetoff's laboratory (12). The Palx3-Luc plasmid expresses the firefly luciferase. The mutant TR*β*1 constructs (I276L, I280S, M313T, R316H, L330S, G344A, G345R, M442T) were generated by *in vitro* site-directed mutagenesis on the pcDNAI/Amp-WT TR*β*1 (QuikChange site-directed mutagenesis kit, Stratagene, La Jolla, CA). All mutant TR*β*1 constructs were verified by direct sequencing.

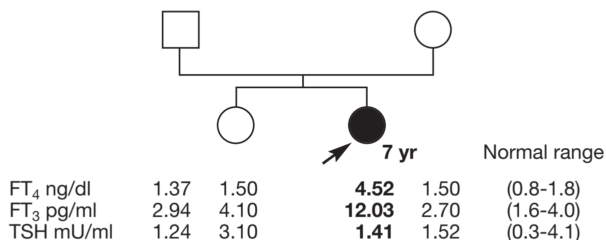

Fig. 1 - *Pedigree and results of the thyroid function tests for the family with a de novo mutation in the* thyroid hormone receptor β *gene (p.M313T).*

Cell culture and transient transfection assays

COS-7 cells (simian virus 40-transformed African green monkey kidney fibroblasts) were grown in Dulbecco's Modified Eagle Medium containing 10% fetal bovine serum at 37 C and 5% CO_2. The assay for transactivation and dominant negative activity has been previously described (13). The pcDNAI/Amp-WT TR*β*1 was transfected at a concentration of 30 ng/well while the Palx3-Luc reporter plasmid was transfected at 1 µg/well. The empty pcDNA 3.1 plasmid was used to adjust the total amount of transfected DNA to 1.6 µg/well. Dominant negative effect was performed at 10^{-7} M of T_3 by transfection of the pcDNAI/Amp-WT TR*β*1 and the plasmid containing the mutant TR*β*1s with the ratios of 1:1 (30:30 ng) and 1:4 (30:120 ng), respectively (13). Firefly luciferase and Renilla-TK luciferase activities were determined sequentially (Dual-luciferase reporter assay system, Promega). Firefly luciferase activity was normalized by Renilla-TK luciferase activity. Experiments were performed twice with triplicate per experiment. Luciferase activity was expressed as fold induction±SEM for T_3-dependent transactivation and percent activity of the WT receptor for dominant negative effect.

RESULTS

Analysis of the *TRβ1* gene by PCR-sequencing revealed that the proband was heterozygous for a T to C transition (ATG to ACG) in exon 9 resulting in a methionine-to-thymine substitution at codon 313 (p.M313T). This was a *de novo* mutation as her parents had a normal thyroid phenotype and did not harbor the mutation (Fig. 2).
This particular mutation has been previously described

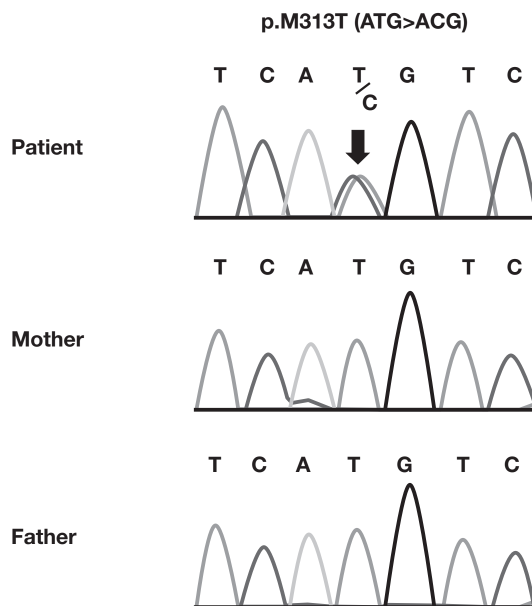

Fig. 2 - *Mutation analysis. An electropherogram of the proband showing a heterozygous missense mutation (an arrow) resulting in a methionine (ATG) to threonine (ACG) substitution at codon 313 (p.M313T) (the upper panel). The identified mutation was not detected in her parents (the middle and lower panels).*

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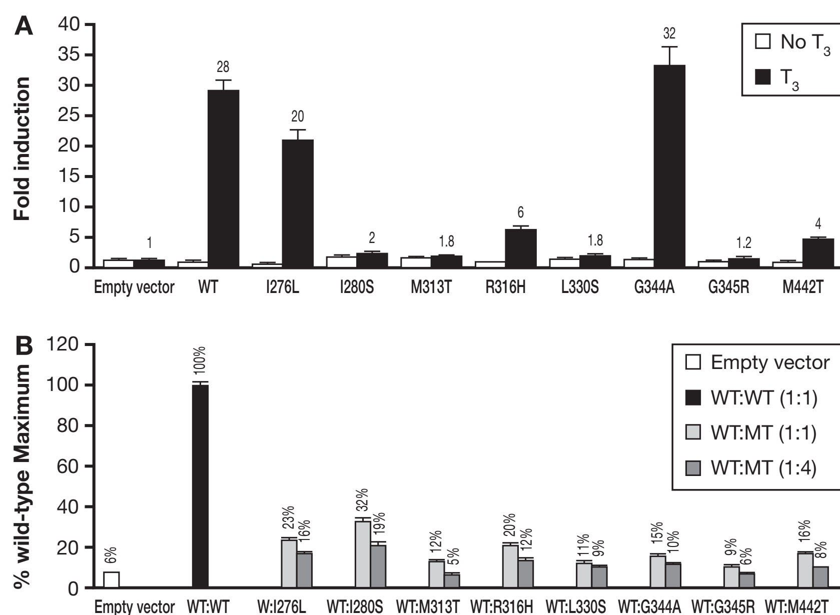

Fig. 3 - *Functional analysis of the mutant thyroid hormone receptor (TR) β1. Panel A shows a T_3-dependent transactivation of the Palx3-Luc reporter in COS-7 cells transfected with different constructs. All except the I276L and G344A mutants showed a significant reduction of the T_3-dependent transactivation activity compared with that of the WT TRβ1. Data were represented in fold induction relative to the luciferase activity of the vector control. Relative stimulation in the presence of T_3 treatment (10^{-7}M of T_3) is indicated above the bars. Panel B showed a dominant negative effect of the mutant TRβ1. At both ratios of all wild type to mutant TRβ1, all mutant TRβ1 exhibited a dominant negative effect in the presence of 10^{-7} M of T_3. The G345R mutant has been shown to have a potent dominant negative effect and therefore was used as a positive control in this study. Firefly luciferase activity was normalized by Renilla-TK luciferase activity. Data were presented as percent activity of the WT receptor. Experiments were performed twice with triplicate per experiment.*

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but never been investigated for its functional significance (14-17). There also remained 5 other uncharacterized mutations (p.I276L, p.I280S, p.L330S, p.G344A and p.M442T) reported in patients with RTH (7-11). Studies using the T_3-dependent transactivation of the Palx3-Luc reporter in COS-7 cells revealed that all except the p.I276L and p.G344A had a significant impairment of T_3-dependent transactivation activity (Fig. 3A). Co-transfection of the wild-type TRβ with each of the mutants demonstrated a significant reduction in T_3-dependent transactivation activity with a dose-dependent manner (Fig. 3B).

DISCUSSION

Mutation analysis of the *TRβ* gene has been used increasingly to allow definite diagnosis of RTH preventing potential misdiagnosis and inappropriate treatment. We identified a *de novo* p.M313T mutation in a Thai patient with clinical and laboratory manifestations suspected of RTH. This mutation has previously been reported in other patients from five unrelated families with different ethnicities (14-17). These patients had different clinical severity ranging from euthyroid state to thyrotoxicosis with variable age of onset. Our patient had goiter, the feature that was noted in all patients with this particular mutation. Other features that were not found in our patient included hyperactivity and thyrotoxicosis. Hyperactivity behavior was reported in 2 unrelated kindreds, one was Caucasian and the other was Chinese (15). Thyrotoxicosis was detected in one family with two affected individuals. The patient inherited the mutation from his mother and developed thyrotoxicosis during neonatal period. His mother had secondary infertility and thyrotoxicosis whose symptoms could be alleviated by treatment with PTU (17). The variation of RTH phenotype among different families harboring the similar mutation suggests that other factors including genetic background are involved in the expression of the phenotype (3, 18).

Elucidating the functional effects of the mutations could confirm their pathogenicity and lead to better understanding of the structure-function relationship. The consequence of the p.M313T mutation on the receptor function has never been evaluated. There are also 5 other uncharacterized mutations in the *TRβ* gene reported in patients with RTH. Each is located in one of the 3 mutational hot spots of the *TRβ* gene. The p.I276L and p. I280S are located in cluster III (amino acids 234-282), the p.L330S and p.G344A in cluster II (310-353), and the p.M442T in cluster I (429-461) (Fig. 4) (3, 19). The p.I276L was detected in a family with 3 members having hyperthyroxinemia with non-suppressed TSH suggesting RTH. All were clinically euthyroid (11). The p.I280S was identified in an individual with severe RTH phenotype. The patient was found to be homozygous or hemizygous for this particular mutation. However, the patient's mother was heterozygous for this mutation and had only goiter (9). The p.L330S mutation was reported in a female patient with goiter and palpitations (7, 20). The p.G344A was detected in a large family with several members affected with RTH. There were substantial variations in clinical presentations with the majority being asymptomatic (10). The p.M442T was found in a family affected with RTH with one member having a diffuse nodular goiter and tachycardia (8).

We performed functional assays for hormone-dependent transactivation activity using the positively-regulated reporter revealing that all mutations except for the p.I276L and p.G344A caused a significant impairment of transactivation activity. Nevertheless, all mutants exhibited dominant negative effect in the presence of high T_3 concentration (10^{-7} M). The functional effect of the p.R316H

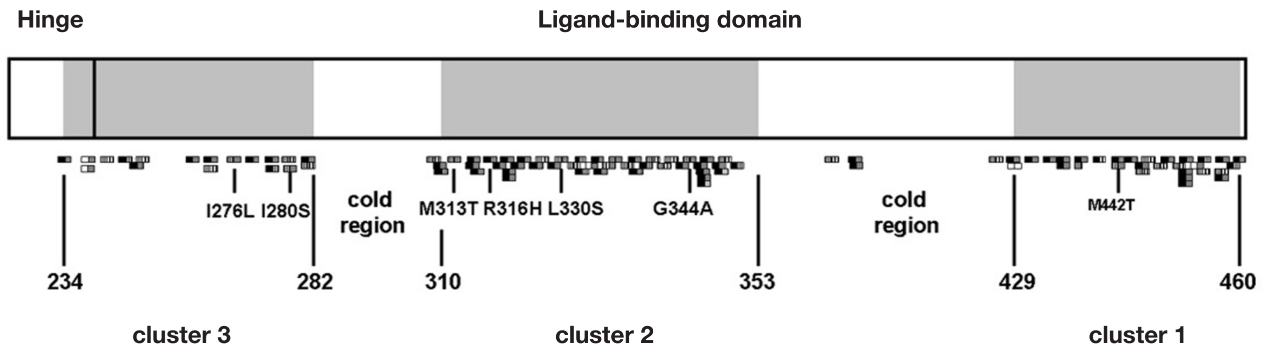

Fig. 4 - *Schematic representation of thyroid hormone (TH) receptor (TR) β1 with location of mutations in individuals with resistance to TH (RTH). The distal end of the hinge region and the ligand-binding domain containing the 3 different mutational "hot spots" are demonstrated [cluster I (amino acids 429-460), cluster II (310-353), and cluster III (234-282)]. At least 124 different mutations have been identified with the majority being the missense/nonsense mutations (19) (http://www.hgmd.cf.ac.uk, accessed July 2010). The location of missense/nonsense mutations reported to date is each indicated by a symbol with two different colors representing its functional effect: ■: reduced T_3-binding affinity; ■: dominant negative effect; □: normal activity; ◫: untested.*

located close to the p.M313T was also performed. Even though there were previous reports of its binding affinity and dominant negative effect (2, 5, 12, 21, 22), one demonstrated a significantly impaired T_3-binding affinity with the lack of dominant negative activity when using the MTV-TRE_{ir}-CAT as a reporter plasmid in a transient transfection assay in Hela cells (21). Our studies showing the relatively weak dominant negative activity of the p.R316H confirmed the results of most previous reports demonstrating its significant impairment of T_3-binding affinity and dominant negative effect. The discrepant results observed in one study could be due to the use of different reporter constructs and cell lines.

Our studies on the p.I276L and p.G344A supported the previous reports that mutations resulting in conservative substitutions retained their transcriptional activities (23, 24). Their pathogenic mechanism is therefore due to dominant negative effect. All the previously identified missense/nonsense mutations in the *TRβ* gene are summarized in Figure 4. Most of them have been characterized with the majority causing reduced T_3-binding affinity or a dominant negative effect.

There is no clear correlation between the clinical severity of RTH and the degree of functional impairment of mutant TRβ (5). However, some different molecular mechanisms responsible for the severe form of RTH have been described including a homozygous complete deletion of both *TRβ* alleles (25) or a homozygous/hemizygous missense mutation (9), heterozygous point mutations causing truncated TRβ (26, 27) and mutations causing inability to recruit the coactivator (13). Of all the mutations characterized in this study, only the p.M313T was identified in an RTH patient with thyrotoxicosis. The pM313T had a significant impairment of transactivation and dominant negative effect which were similar to the p.G345R, one of the most strong mutant *TRβ* associated with a severe RTH phenotype (5). Comparing with the p.G345R, the p.I276L, p.I280S, and p.R316H mutants that were identified in RTH patients with a mild phenotype had a lesser dominant negative effect while the p.L330S, p.G344A, p.M442T that were identified in RTH families with clinical variability including a severe phenotype had no significant difference in the level of dominant negative activity.

Even though the clinical presentation of RTH patients does not always correlate with the functional impairment of the mutant TRβ as demonstrated by some studies (28, 29), others have shown a correlation between the clinical severity of RTH and functional impairment in some mutant TRβ (5, 13). This study provided more TRβ mutants with a possible correlation. It remains possible that type and location of the mutations and tissue-specific cofactors have a major role in determining the clinical severity. Further studies to elucidate additional factors influencing the RTH phenotype are needed.

Our studies revealed the pathogenic mechanism of the uncharacterized mutations and confirmed the dominant negative effect as a major mechanism of RTH. Some causative *TRβ* mutations with a dominant negative effect can preserve their T_3-dependent transactivation activity. To gain further insight of the structure-function relationship of the receptor, further studies are still required.

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CONCLUSION

In conclusion, this study has identified a Thai patient with a *de novo* p.M313T mutation in the *TRβ* gene and further elucidated its pathogenic mechanism. In addition, 5 different uncharacterized known mutations were explored. Even though not all of the mutant TRβ1 exhibited a significant impairment of T_3-induced transactivation, all these mutant TRβ1 showed a dominant negative effect on co-transfection with the wild-type TRβ1. Our studies provide a strong support that interfering with the T_3-mediated transcriptional activation of the wild-type TRβ1 independent of the inability to activate transcription is a major pathogenic mechanism causing RTH.

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REFERENCES

1. Refetoff S, Weiss RE, Usala SJ. The syndromes of resistance to thyroid hormone. Endocr Rev 1993, 14: 348-99.
2. 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 1994, 94: 506-15.
3. Yen PM. Physiological and molecular basis of thyroid hormone action. Physiol Rev 2001, 81: 1097-142.
4. Yen PM, Chin WW. Molecular mechanisms of dominant negative activity by nuclear hormone receptors. Mol Endocrinol 1994, 8: 1450-4.
5. Hayashi Y, Weiss RE, Sarne DH, et al. Do clinical manifestations of resistance to thyroid hormone correlate with the functional alteration of the corresponding mutant thyroid hormone-beta receptors? J Clin Endocrinol Metab 1995, 80: 3246-56.
6. 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: 85-94.
7. Ditudompo S, Ongphiphadhanakul B, Chanprasertyotin S, Rajatanavin R. A de novo L330S point mutation in thyroid hormone receptor beta gene in a Thai female with resistance to thyroid hormone. Endocr J 1999, 46: 825-9.
8. Bayer Y, Fasshauer M, Paschke R. The novel missense mutation methionine 442 threonine in the thyroid hormone receptor beta causes thyroid hormone resistance: a case report. Exp Clin Endocrinol Diabetes 2004, 112: 95-7.
9. Frank-Raue K, Lorenz A, Haag C, et al. Severe form of thyroid hormone resistance in a patient with homozygous/hemizygous mutation of T3 receptor gene. Eur J Endocrinol 2004, 150: 819-23.
10. Kvistad PH, Løvås K, Boman H, Myking OL. Retarded bone growth in thyroid hormone resistance. A clinical study of a large family with a novel thyroid hormone receptor mutation. Eur J Endocrinol 2004, 150: 425-30.
11. Lam CW, On-Kei Chan A, Tong SF, Shek CC, Cheung Tiu S. DNA-based diagnosis of thyroid hormone resistance syndrome: a novel THRB mutation associated with mild resistance to thyroid hormone. Clin Chim Acta 2005, 358: 55-9.
12. 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 1994, 94: 607-15.
13. Lado-Abeal J, Dumitrescu AM, Liao XH, et al. A de novo mutation in an already mutant nucleotide of the thyroid hormone receptor beta gene perpetuates resistance to thyroid hormone. J Clin Endocrinol Metab 2005, 90: 1760-7.
14. Kijima H, Kubo M, Ishizuka T, Kakinuma M, Koike T. A novel missense mutation in the thyroid hormone receptor beta gene in a kindred with resistance to thyroid hormone. Hum Genet 1996, 97: 407-8.
15. Refetoff S, Tunca H, Wilansky DL, Mussey VC, Weiss RE. Mutation in the thyroid hormone receptor (TR) beta gene (M313T) not previously reported in two unrelated families with resistance to thyroid hormone (RTH). Thyroid 1996, 6: 571-3.
16. di Fulvio M, Chiesa AE, Baranzini SE, Gruñiero-Papendieck L, Masini-Repiso AM, Targovnik HM. A new point mutation (M313T) in the thyroid hormone receptor beta gene in a patient with resistance to thyroid hormone. Thyroid 1997, 7: 43-4.
17. Blair JC, Mohan U, Larcher VF, et al. Neonatal thyrotoxicosis and maternal infertility in thyroid hormone resistance due to a mutation in the TRbeta gene (M313T). Clin Endocrinol (Oxf) 2002, 57: 405-9.
18. Weiss RE, Refetoff S. Resistance to thyroid hormone. Rev Endocr Metab Disord 2000, 1: 97-108.
19. 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: 277-305.
20. Pohlenz J, Wildhardt G, Zabel B, Willgerodt H. Resistance to thyroid hormone in a family caused by a new point mutation L330S in the thyroid receptor (TR) beta gene. Thyroid 1997, 7: 39-41.
21. Geffner ME, Su F, Ross NS, et al. An arginine to histidine mutation in codon 311 of the C-erbA beta gene results in a mutant thyroid hormone receptor that does not mediate a dominant negative phenotype. J Clin Invest 1993, 91: 538-46.
22. Persani L, Asteria C, Tonacchera M, et al. Evidence for the secretion of thyrotropin with enhanced bioactivity in syndromes of thyroid hormone resistance. J Clin Endocrinol Metab 1994, 78: 1034-9.
23. Tone Y, Collingwood TN, Adams M, Chatterjee VK. Functional analysis of a transactivation domain in the thyroid hormone beta receptor. J Biol Chem 1994, 269: 31157-61.
24. 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 U S A 1997, 94: 248-53.
25. 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 1992, 74: 49-55.
26. Behr M, Ramsden DB, Loos U. Deoxyribonucleic acid binding and transcriptional silencing by a truncated c-erbA beta 1 thyroid hormone receptor identified in a severely retarded patient with resistance to thyroid hormone. J Clin Endocrinol Metab 1997, 82: 1081-7.
27. Phillips SA, Rotman-Pikielny P, Lazar J, et al. Extreme thyroid hormone resistance in a patient with a novel truncated TR mutant. J Clin Endocrinol Metab 2001, 86: 5142-7.
28. Sakurai A, Takeda K, Ain K, et al. Generalized resistance to thyroid hormone associated with a mutation in the ligand-binding domain of the human thyroid hormone receptor beta. Proc Natl Acad Sci U S A 1989, 86: 8977-81.
29. Usala SJ, Tennyson GE, Bale AE, et al. A base mutation of the C-erbA beta thyroid hormone receptor in a kindred with generalized thyroid hormone resistance. Molecular heterogeneity in two other kindreds. J Clin Invest 1990, 85: 93-100.

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