

Resistance to Thyroid Hormone with Missense Mutation (V349M) in the Thyroid Hormone Receptor Beta Gene

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Resistance to thyroid hormone (RTH) is a syndrome characterized by reduced sensitivity to the thyroid hormone. It is generally caused by mutations in the thyroid hormone receptor β (TR β) gene. On the basis of its clinical features, two different forms of this syndrome have been described: generalized resistance and pituitary resistance. A total of 122 TR β gene mutations have been identified thus far. A 38-year-old woman presented with intermittent palpitation. Thyroid function tests revealed elevated levels of free T₄ and TSH. TSH α -subunit levels were 0.41 mIU/mL, and magnetic resonance images of the sellar region evidenced no abnormal findings. The TSH response to TRH stimulation was found to be normal. The sequence analysis of the TR β gene verified a missense mutation in exon 11, and the observed amino acid alteration was a substitution of a valine for a methionine at codon 349. We report the first case of a woman with RTH, which was found to be caused by a missense mutation (V349M) in the TR β gene.

Key Words : Thyroid hormone resistance syndrome; Thyroid hormone receptors beta; Mutation; Missense

INTRODUCTION

Thyroid hormone resistance (RTH) syndrome is a rare disorder, which is characterized by reduced target tissue responsiveness to circulating free-thyroid hormones. Thyroid hormone resistance was initially described by Refetoff et al. in 1967¹. Typically, patients evidence elevated serum levels of free T₄ and T₃ associated with normal or slightly elevated TSH². On the basis of the clinical features, at least two different forms of RTH have been described: generalized resistance to thyroid hormone (GRTH), in which patients are asymptomatic with a few clinical signs, and pituitary resistance to thyroid hormone (PRTH), in which patients present with some thyrotoxicosis-associated signs and symptoms. However, there is a wide overlap in the symptoms and signs evidenced by individuals with GRTH and

PRTH³. Although the clinical expression of this syndrome is heterogenous, goiter is the most common clinical finding which brings the individual to medical attention³, and the classic features include attention-deficit hyperactivity disorder, delays in growth, and tachycardia¹. Resistance to thyroid hormone is generally transmitted in an autosomal dominant manner. However, sporadic *de novo* cases are also common, although recessive inheritance is rare¹. The linkage between RTH and the TR β gene was elucidated in 1988⁴. Since that time, approximately 100 mutations have been detected in this gene^{1, 5}, which are clustered primarily in *hot spots* in the T₃-binding domain (exons 8, 9 and 10)⁶⁻⁸. In this study, we report the first case in Korea of a woman with PRTH caused by a missense mutation (V349M) in the TR β gene.

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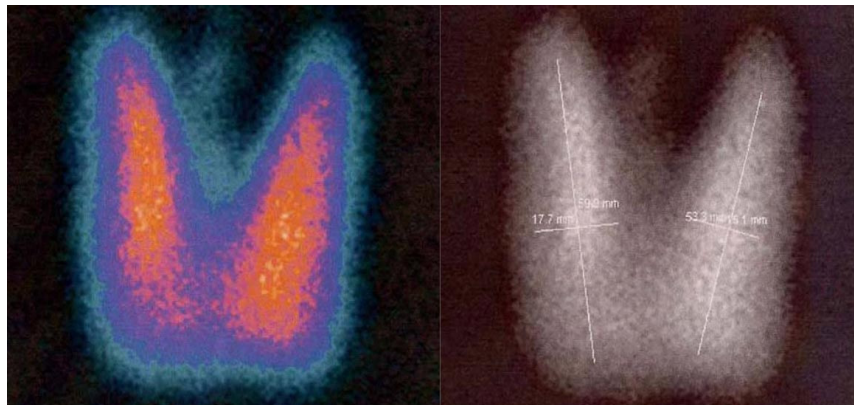
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Table 1. Hormonal parameters in a women with resistance to thyroid hormone

Daily drug dose and duration of administration	fT ₄ (0.7-1.8 ng/dL)	T ₃ (80-200 ng/dL)	TSH (0.1-4.2 μ IU/mL)
2005/1	2.51	163	14.24
2005/5 (methimazole 10 mg for 8 weeks)	1.89	224	33.59
2005/8	3.53	300	3.0
2005/11 (atenolol 100 mg for 4 weeks)	3.76	250	1.9

Table 2. Thyroid-stimulating hormone (TSH) response to Thyrotropin-release hormone (TRH) 200 μ g stimulation

	Basal	30 min	60 min	90 min	120 min
TSH (μ IU/mL)	2.3	30.8	19.0	12.6	7.6

**Figure 1.** ^{99m}Tc thyroid scan reveals diffuse enlargement of both thyroid glands without abnormal focal lesions.

CASE REPORT

A 38-year-old Korean woman was referred to us in June 1998, complaining of intermittent palpitation that had persisted for 2 years. Her treatment was initiated under the diagnosis of hyperthyroidism in June 1996 at a primary care clinic, and after a six-month treatment, she discontinued medication. When first seen at our clinic, she weighed 53 kg, her height was 158 cm, her blood pressure was 130/80 mmHg, and her pulse rate was 90 beats/min. The patient had no family history of thyroid diseases. The patient's thyroid gland was diffusely symmetrically enlarged, and no thrill, bruit, or exophthalmos was detected. At that time, her thyroid function tests revealed free T₄, 2.60 ng/dL (range, 0.7-1.8); T₃, 150 ng/dL (range, 80-200); TSH, 3.0 μ IU/mL (range, 0.1-4.2); anti-thyroglobulin (TG) antibody, 20.34 U/mL (<0.3); and anti-microsomal antibody, 11.30 U/mL (<0.3).

After three visits, the patient was lost to follow-up. In December 2004, she visited a primary care clinic, and her thyroid function tests revealed free T₄, 2.51 ng/dL; T₃, 163 ng/dL; and TSH 14.24 μ IU/mL. In February 2005 she received an anti-thyroid drug, methimazole 10 mg, due to suspicion of

diffuse goiter. She was again referred to us in July 2005 for further evaluation and treatment for diffuse goiter. Thyroid function tests, which were conducted at a primary care clinic in March 2005, revealed free T₄, 1.89 ng/dL; T₃, 224 ng/dL; and TSH, 33.59 μ IU/mL. We then discontinued methimazole, and the patient was scheduled to take thyroid function tests after one month. Thyroid function tests were conducted one month later, and revealed the following: free T₄, 3.53 ng/dL; T₃, 300 ng/dL; TSH, 3.0 μ IU/mL; and thyroxine-binding globulin (TBG), 23.08 μ g/mL (range, 11.3-28.9). Tests for thyroid auto-antibodies revealed TG antibody, 68.04 U/mL; anti-microsomal antibody, >100 U/mL; thyroid stimulating immunoglobulin (TSI), 0% (<15); and T₃ and T₄ autoantibodies, negative. Thereafter, the patient was treated with atenolol 100 mg for 4 weeks. Four weeks later, she had no palpitation and her medication was discontinued. Thyroid scans indicated that the thyroid gland was diffusely enlarged, but we noted no abnormal focal lesions (Figure 1). Basal serum TSH levels were abnormally high, and increased to a significant degree after stimulation with 200 μ g of TRH (Table 1). The level of TSH β -subunit was 0.41 mIU/mL (range, 0-0.9), TSH α -subunit/TSH was 1, and sex hormone-

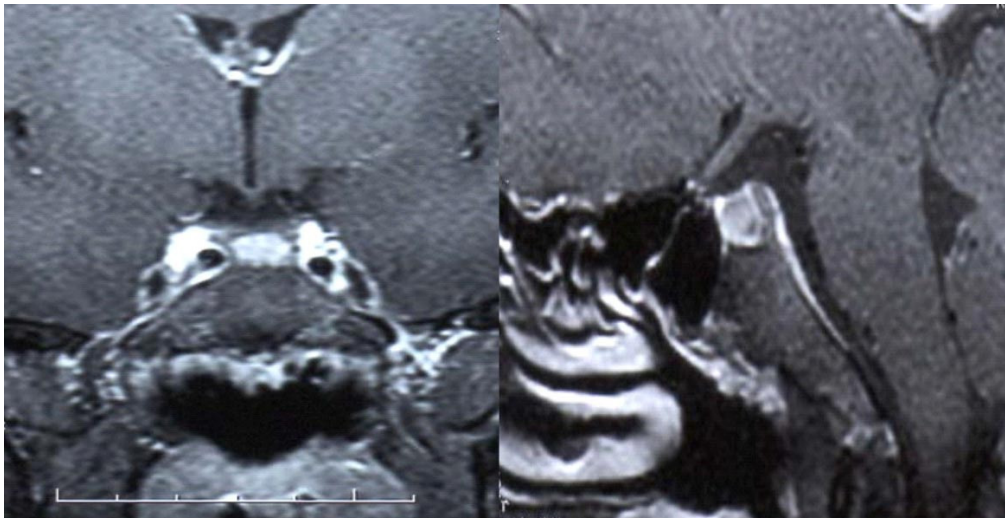


Figure 2. Sellar MRI shows normal pituitary glands.

binding globulin (SHBG) was 39.23 nmol/L (range, 30-100). MR imaging of the sellar lesion evidenced no abnormal findings (Figure 2). For the next diagnostic plan, we conducted a sequence analysis of the TR β gene. The result revealed a missense mutation in exon 11 and an amino acid alteration—namely, a substitution of valine for methionine at codon 349 (Figure 3). On the basis of these results, she was ultimately diagnosed with thyroid hormone resistance syndrome, and she has been followed up with periodic thyroid function tests.

DISCUSSION

Thyroid hormone resistance syndrome is characterized by elevated levels of circulating free thyroid hormone, inappropriate TSH secretion, and reduced peripheral tissue responses to the activity of iodothyronine. Inappropriate secretion of TSH and the coexistence of elevated serum thyroid hormone and normal TSH levels has been noted in several situations, including abnormal thyroid hormone transport, TSH-secreting pituitary neoplasms, and pituitary or peripheral resistance to thyroid hormones^{9,10}.

RTH is the consequence of mutations in the gene of the thyroid hormone receptor (TRs). The mutant TR interferes with the activity of normal TR to induce the clinical syndrome¹¹. As RTH patients present with elevated thyroid hormone levels and goiter, frequently accompanied by some manifestations of thyrotoxicosis, the condition is often misdiagnosed as Graves' disease. However, exophthalmos has never been identified as a feature of RTH, and thyroid auto-antibodies have been detected only in approximately 4% of patients¹². By way of contrast, thyroid hormone hypersecretion as the result of stimulating auto-antibodies (Graves' disease) or hyperfunctioning thyroid

tissue (autonomous single or multinodular goiter) is uniformly associated with the inhibition of TSH secretion, resulting in unmeasurable serum TSH levels¹³.

Clinically, thyroid hormone resistance can be divided into two entities: GRTH and PRTH¹¹. Both GRTH and PRTH are rare diseases, occurring at any age and with no sex predilection. In general, diagnoses of PRTH are made largely on the basis of the presence of the clinical signs and symptoms of hyperthyroidism¹³. Comprehensive assessments utilizing biochemical and physiological indices of thyroid hormone action are useful, but are limited by their lack of precision. Moreover, they also evidence an overlap between the values recorded in cases of GRTH and PRTH¹¹. No differences in the absolute levels of TSH or free thyroid hormone are observed in GRTH patients as opposed to PRTH patients. Stimulatory and inhibitory tests have also been conducted in GRTH and PRTH patients, in order to evaluate the pituitary-thyroid axis in a dynamic manner. The TSH response to TRH is normal, or even exaggerated, and is prolonged in all GRTH and PRTH patients². A molecular mechanism to explain these two clinical phenotypes has proven elusive, and many authors have concluded that they are part of a spectrum of the same disorder¹³.

TRs belong to the superfamily of ligand-dependent transcription factors. TRs are encoded by the thyroid hormone receptor α gene (THRA) and the thyroid hormone receptor β gene (THRB), which are located on chromosomes 17 and 3, respectively. The expression of TRs occurs in a tissue-dependent fashion. Although THRA1 and THRB1 are expressed ubiquitously, THRA1 is expressed predominantly in the heart, bone, and brain, whereas TR β 1 is expressed more abundantly in the liver, kidney, and thyroid. THRB2 expression is limited to the pituitary gland, hypothalamus, retina, and inner ear, and

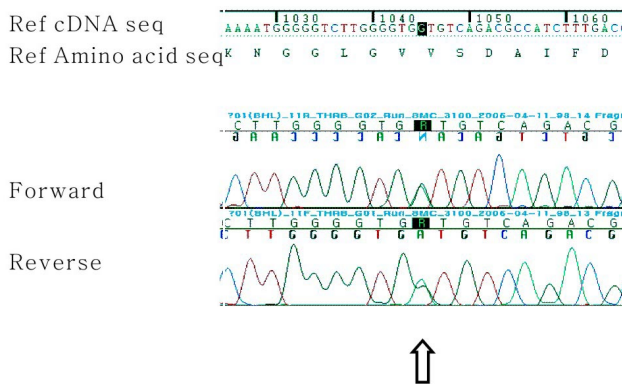


Figure 3. The sequence analysis of the thyroid hormone receptor β gene (THRB) in the patient. Automated direct sequencing of exon 11 reveals a heterozygous G for A substitution (arrow), resulting in a Val349Met missense mutation (c.1045G>A; p.Val 349Met).

THRB3 expression occurs principally in the heart and kidney¹⁴. One of the most salient reasons for recognizing RTH is that its management differs from that of other common forms of thyroid dysfunction. In addition, discrimination between GRTH and PRTH using clinical criteria remains useful, as the management of the two states differs. Patients with unequivocal peripheral or pituitary resistance should not be treated with antithyroid agents, as any reduction in elevated thyroid hormones may aggravate symptoms, reduce growth and development, and exacerbate goiter. Patients who present with apparent selective pituitary resistance are the most difficult to manage. Many of the patients with peripheral resistance appear to benefit from further increases in serum thyroid hormone levels as the result of cautious exogenous administration of T₄ or T₃. At a minimum, such therapy tends to reduce serum TSH levels and goiter to some degree¹⁵.

With the increasing availability of sensitive and specific TSH radioimmunoassays, a greater number of these patients are being detected. It is important to remember that these patients may display only minimal elevation of serum TSH. On rare occasions, TSH may be within normal ranges, but may still be inappropriately high, despite elevated free thyroid hormone levels.

REFERENCES

- 1) Brucker-Davis F, Skarulis MC, Grace MB, Benichou J, Hauser P, Wiggs E, Weintraub BD. Genetic and clinical features of 42 kindreds with resistance to thyroid hormone. *Ann Intern Med* 123:572-583, 1995
- 2) Refetoff S, Weiss RE, Usala SJ. The syndromes of resistance to thyroid hormone. *Endocr Rev* 14:348-399, 1993
- 3) Anselmo J, Refetoff S. Regression of a large goiter in a patient with resistance to thyroid hormone by every other day treatment with triiodothyronine. *Thyroid* 14:71-74, 2004
- 4) Usala SJ, Bale AE, Gesundheit N, Weinberger C, Lash RW, Wondisford FE, McBride OW, Weintraub BD. Tight linkage between the syndrome of generalized thyroid hormone resistance and the human *c-erbA* beta gene. *Mol Endocrinol* 2:1217-1220, 1988
- 5) Beck-Peccoz P, Chatterjee VK, Chin WW, DeGroot LJ, Jameson JL, Nakamura H, Refetoff S, Usala SJ, Weintraub BD. Nomenclature of thyroid hormone receptor beta-gene mutations in resistance to thyroid hormone: consensus statement from the first workshop on thyroid hormone resistance, July 10-11, 1993, Cambridge, United Kingdom. *J Clin Endocrinol Metab* 78:990-993, 1994
- 6) Blair JC, Mohan U, Larcher VF, Rajanayagam O, Burrin JM, Perry LA, Grossman AB, Chatterjee VK, Savage MO. Neonatal thyrotoxicosis and maternal infertility in thyroid hormone resistance due to a mutation in the TRbeta gene (M313T). *Clin Endocrinol* 57:405-409, 2002
- 7) di Fulvio M, Chiesa AE, Baranzini SE, Gruniero-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* 7:43-44, 1997
- 8) 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* 6:571-573, 1996
- 9) Hamon P, Bovier LM, Robert M, Peynaud D, Pugeat M, Orgiazzi J. Hyperthyroidism due to selective pituitary resistance to thyroid hormones in a 15-month-old boy: efficacy of D-thyroxine therapy. *J Clin Endocrinol Metab* 67:1089-1093, 1988
- 10) Master PA, Simons RJ. Clinical use of sensitive assays for thyroid-stimulating hormone. *J Gen Intern Med* 11:115-127, 1996
- 11) Safer JD, Langlois MF, Cohen R, Monden T, John-Hope D, Madura J, Hollenberg AN, Wondisford FE. Isoform variable action among thyroid hormone receptor mutants provides insight into pituitary resistance to thyroid hormone. *Mol Endocrinol* 11:16-26, 1997
- 12) Kourides IA, Pekonen F, Weintraub BD. Absence of thyroid-binding immunoglobulins in patients with thyrotropin-mediated hyperthyroidism. *J Clin Endocrinol Metab* 51:272-274, 1980
- 13) Beck-Peccoz P, Chatterjee VK. The variable clinical phenotype in thyroid hormone resistance syndrome. *Thyroid* 4:225-232, 1994
- 14) Cheng SY. Thyroid hormone receptor mutations and disease: beyond thyroid hormone resistance. *Trends Endocrinol Metab* 16:176-182, 2005
- 15) Refetoff S, Salazar A, Smith TJ, Scherberg NH. The consequences of inappropriate treatment because of failure to recognize the syndrome of pituitary and peripheral tissue resistance to thyroid hormone. *Metabolism* 32:822-834, 1983