□ Case Report □

Identification of a *de novo* mutation (H435Y) in the THRB gene in a Korean patient with resistance to thyroid hormone

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The syndrome of resistance to thyroid hormone (RTH) is characterized by reduced tissue sensitivity to thyroid hormone (TH). In the majority of subjects, RTH is caused by mutations in the thyroid hormone receptor beta (TRβ) gene, located on the chromosome locus 3p24.3. RTH is inherited in an autosomal dominant manner. The clinical presentation of RTH is variable, but common features include elevated serum levels of thyroid hormone (TH), a normal or slightly increased thyrotropin (thyroid stimulating hormone, TSH) level that responds to thyrotropin releasing hormone (TRH), and goiter. We report a 4 year-old girl, who was clinically euthyroid in spite of high total and free T_4, and T_3 concentrations, while TSH was slightly increased. Sequence analysis of the thyroid hormone receptor beta gene (*THRB*) confirmed a heterozygous C to T change at nucleotide number 1303, resulting in a substitution of histidine by tyrosine at codon 435 (H435Y). Further analysis of her parents revealed that the H435Y variation was a *de novo* mutation since neither parents had the variation. Her parents' TH and TSH levels were within normal range. **(Korean J Pediatr 2007; 50:576-579)**

Key Words : Resistance to thyroid hormone (RTH), Thyroid hormone receptor beta (TRβ), Thyroid hormone receptor beta gene (THRB)

Introduction

Resistance to thyroid hormone (RTH) is a rare inherited syndrome of tissue hyporesponsiveness to thyroid hormone (TH) of variable degree. The common characteristic features of the syndrome of RTH include (a) elevated serum levels of free T_4 and T_3, (b) a normal or slightly increased thyrotropin (thyroid stimulating hormone, TSH) level that responds to thyrotropin releasing hormone (TRH), (c) an absence of the usual symptoms and metabolic consequences of TH excess, and (d) goiter. The phenotype, in patients with RTH, varies considerably, and the clinical diagnosis may be difficult because affected persons do not have the typical clinical stigmata of a thyroid dependent metabolic disturbance.

We report a case of a 4 year-old female with RTH who had a heterozygous missence mutation in codon 435 of THRB gene (H435Y), caused by a substitution of a histidine by a tyrosine. The patients has not family history of RTH.

Case report

A 4 year-old girl presented poor oral intake and weight gain (Fig. 1). She had a good activity, but felt tired easily and was sensitive. She was thin, with birdlike face, and had a small goiter. However, she had no history of heat intolerance, excessive sweating, tremors, insomnia, palpitations, hyperactivity, constipation, or developmental delay.

She was born at 37 weeks of gestation with 2,580 grams of birth weight, after an uneventful pregnancy that was without perinatal complications. Her weight was 12 kg (3-10 percentiles), and height was 102 cm (50 percentile). Blood pressure (100/60 mmHg) and pulse rate (100 beats/ min) were within the normal range for her age. Developmental quotient by Korean infant and toddler development screening

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test was above 100%.

Laboratory examinations revealed a highly elevated total and free TH and unsuppressed TSH values, as well as a mildly elevated PRL (Table 1). Thyroid autoantibodies against thyroperoxidase, thyroglobulin and TSH receptor were negative. Thyroxine binding globulin, free α subunit, sex hormone binding globulin (SHBG) were within normal range. Peak TSH after 30 min of TRH (5-7 μg/kg IV) test was 20.8 mIU/mL and peak Prolactin (PRL) after TRH was 64.5 ng/mL.

Other findings included : hemoglobin 13.5 g/dL, hematocrit 39.7%, and white blood cell count 10,500/μL with normal differentials. Serum electrolytes, renal function test, liver function test were within normal range.

Electrocardiography was normal. Bone age was 3 years 6 months at the chronological age of 4 years and 2 months. Thyroid ultrasonography showed normal structure and volume of the gland and thyroid scan was unremarkable. Brain magnetic resonance image did not show any mass in the hypothalamic-pituitary area.

Direct sequencing of THRB gene disclosed a heterozygous C to T transition at nucleotide number 1303 (c.1303C>T), resulting in a substitution of histidine by tyrosine at codon 435 (H435Y; Fig. 2). Her parents did not have this variation and their TH and TSH levels were within the normal range. The H435Y variation has not been observed in 100 control chromosomes.

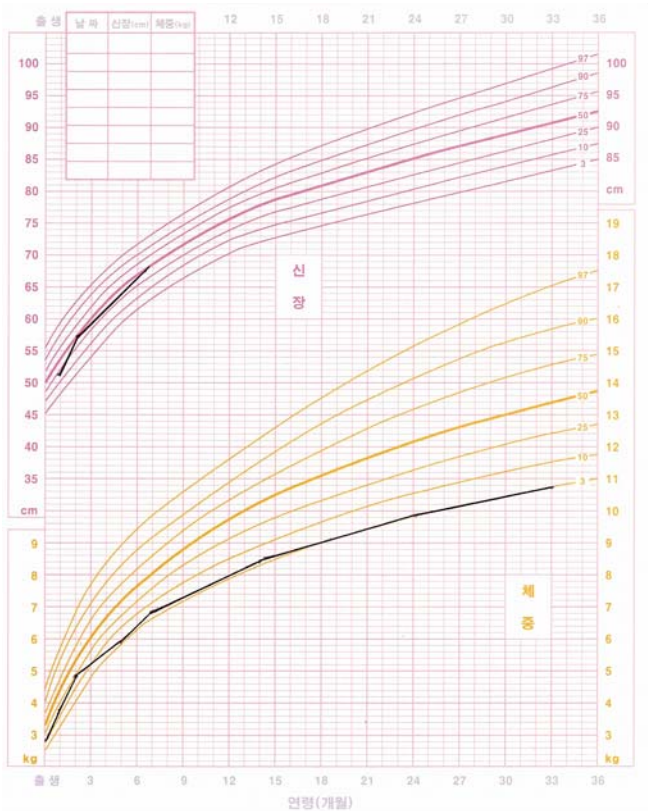

Fig. 1. Growth chart.

Table 1. Results of Thyroid Function Test and Prolactin

	4yr 2m	4yr 4m	4yr 6m	Reference range
TSH	3.85	5.54	6.73	0.5-4.8 uIU/mL
T_4	>24.86	>24.86		5.5-12.8 ug/dL
free T_4	7.03	6.95	4.97	0.8-2.2 ng/dL
T_3	3.70	4.86	4.12	1.19-2.18 ng/mL
free T_3	5.67	13.24		2.1-4.8 pg/mL
prolactin		27.7	32	0-25 ng/mL

Discussion

The precise incidence of syndrome of resistance to thyroid hormone is unknown. A limited neonatal survey by measuring blood T_4 concentration suggested an occurrence at a rate of 1 case per 40,000 live births[1]. RTH is generally

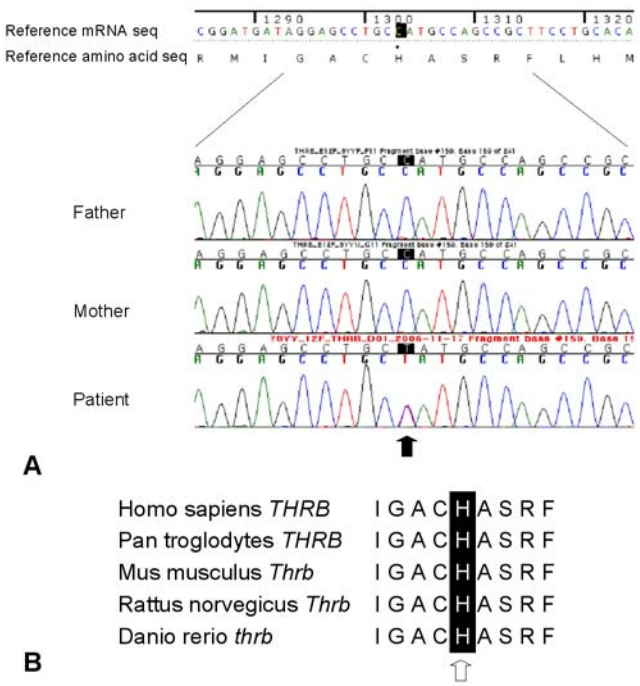

Fig. 2. A) Direct sequencing of thyroid hormone receptor-beta (THRB) gene revealed a novel *de novo* H435Y mutation in the patient (filled arrow; c.1303C>T based on the reference mRNA sequence, NM_000461). The patient's parents did not have the mutation. B) The H435Y mutation occurred at an evolutionally conserved amino acid in the ligand-binding domain of nuclear hormone receptor (open arrow).

inherited in an autosomal dominant manner. Familial occurrence of RTH has been documented in approximately 75% of case[2].

The majority of individuals are completely asymptomatic. Manifestations are variable from one patients to another. The common clinical findings are goiter, tachycardia, attention deficit disorder, learning disability, and delayed bone age. Less common findings are reduced intelligence quotient, short stature, and hearing loss. Not uncommonly, individuals have symptoms of both TH deficiency and excess[3].

TRs are encoded by the TR α and TR β genes located on chromosome 17 and 3, respectively. Alternative splicing of the primary transcripts of each gene give rises to TR isoforms : Four T3 binding proteins (β1, β2, β3 and α1) and two non-T3 binding proteins (α2, α3)[4]. The distribution of TR isoforms varies from tissue to tissue. Although TR β1 is widely distributed in the body, TR α1 is predominantly expressed in the heart. Liver function is principally TR β dependent, but heart rate and metabolism have a major TR α dependency. RTH patients are usually euthyroid, though some may show hyperthyroid features such as tachycardia due to stimulation of cardiac TR α1 as opposed to TR β where there is resistance[3].

TR consists of 3 functional domains : an amino(N)-terminal transactivation domains, a DNA-binding domain, and a carboxyl(C)-terminal ligand binding and dimerization domain. These T3 binding TRs are highly homologous, except in the N terminal A/B domains[5]. TRs form homodimers or heterodimers with the retinoid X receptors (RXRs) and bind to specific DNA sequences termed thyroid hormone response elements (TREs). In the absence of T_3, TR homodimers and heterodimers are associated with corepressors that repress or silence the transcription of genes. Gene transcription is stimulated by the binding of T_3 to TRs, which releases the corepressors and recruits nuclear coactivators[6].

About 90% of RTH patients carry mutations in their TR β gene[7-10]. Most patients are heterozygous, with only one mutated TR β gene, the clinical symptoms are mild. RTH is not simply the consequence of a reduced amount of functional TR but is caused by the interference of the mutant TR with the function of the wild type TR (dominant negative manner)[11]. This involves the occupation of a TRE by a mutant TR that has one of the following properties alone or in combination : impaired T3 binding activity; increased affinity for the corepressors; and reduced ability to recruit coactivators necessary to enhance gene transcription[2]. In addition, subjects with the same mutations, even belonging to the same family, showed different degrees of RTH. This variation is likely due to the magnitude of the functional impairment of the mutant TR β and relative level of tissue expression of the mutant TR β and other unidentified co-factors (coactivators and corepressors). Genetic variability of factors other than TR may modulate the phenotype of RTH[12].

Currently, greater than 100 mutations have been reported in the TR β gene, whereas none have been found, to date, in the TR α genes[2]. The mutations are localized in the ligand-binding domain (LBD) and adjacent hinge region of the TR β gene[2]. Mutations in the TR α or TR β genes were not found in about 10% of family with RTH[13, 14].

In this case, direct sequencing of THRB gene disclosed a heterozygous C to T transition at nucleotide number 1303 resulting in a substitution of histidine by tyrosine at codon 435 (H435Y). Further analysis of her parents' revealed that the H435Y variation was a de novo mutation simnce both parents did not have the variation. Her parents' TH and TSH levels were within normal range, as expected. Although this variation has not been identified in patients with RTH, two mutations affecting the same codon such as His435Leu and His435Gln have been reported previously[15].

The differential diagnosis includes all possible causes of hyperthyroxinemia, such as TSH-secreting pituitary adenoma, thyroxine binding protein abnormalities, artifactual increase in levels of TSH due to heterophilic antibodies.

The course of the disease is as variable as its presentation. Some have normal growth and development, and lead a normal life. Others have variable degrees of mental and growth retardation[2].

No treatment is available to fully correct the defect causing RTH. The majority of individuals adequately compensate for the abnormal TR β through increased TH secretion. It is more difficult than the treatment of patients with RTH who have apparent hypothyroidism at the level of peripheral tissues but are not accompanied by an increase in the serum TSH concentration. In such individuals, the judicious administration of supraphysiological doses of TH requires careful monitoring. Because the dose varies greatly among cases[16], it should be individually determined by assessing tissue responses.

Patients with more severe thyrotroph resistance and symptoms of thyrotoxicosis may require therapy such as atenolol, antianxiety drugs. The TH analogue, TRIAC (3,5,3'-triiodo-

thyroacetic acid) has been used to decrease the serum TSH and TH levels, to reduce goiter size, and to alleviate some of the symptoms attributed to the effect of TH on peripheral tissues[17].

The patient of this case has shown no increase in goiter and no aggravation in the symptoms even without any medication for 6 months after initial diagnosis.

한 글 요 약

갑상선호르몬 수용체 베타 유전자 돌연변이(H435Y)가 확인된 갑상선호르몬 저항성 증후군 1례

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갑상선 호르몬 저항성 증후군은 갑상선 호르몬에 대한 조직의 반응이 감소되어 나타나는 드문 유전 질환이다. 대부분은 갑상선 호르몬 수용체 (TR) 유전자의 돌연변이로 인한 갑상선 호르몬 수용체의 결함에 의한다. TR 유전자의 변이는 일반적으로 이형접합성이며 상염색체 우성 유전 양상을 보인다. 혈청 갑상선 호르몬 수치가 증가되어 있음에도 불구하고 혈청 갑상선 자극호르몬 수치가 억제되지 않으며, 임상 양상은 다양하다.

본 증례는 경미한 갑상선종, 총 및 유리 T_4, T_3의 증가, 정상 범위의 TSH 소견을 보이는 4세 여아로서 TR 유전자 분석에서 과오돌연변이(H435Y)를 확인하였다. 부모에서는 돌연변이가 관찰되지 않았으며, 갑상선 기능도 정상이었다. 특별한 투약 없이 추적 관찰 중에 갑상선종의 증가나 다른 증상의 악화는 없는 상태이다.

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