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CASE REPORT

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Resistance to thyroid hormone caused by heterozygous mutation of thyroid hormone receptor B gene c.G1378A: Report of one Chinese pedigree and literature review

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Abstract

The same thyroid hormone receptor B gene (THRB) mutation led to thyroid hormone resistance with different clinical manifestations in the kindreds.

KEYWORDS

mutation, resistance to thyroid hormone, thyroid hormone receptor B

1 | INTRODUCTION

A 30-year-old female patient with clinical manifestations of palpitations and goiter showed elevated thyroid hormone with nonsuppressed TSH. A heterozygous mutation of the THRB exon10 c. G1378A (p. E460K) was identified in the proband and her kindreds. However, the clinical features in the kindreds were different from the probands.

Resistance to thyroid hormone (RTH) is a rare syndrome caused by reduced sensitivity of target tissues to thyroid hormone,[1] which is characterized by elevated thyroid hormone with "inappropriately" nonsuppressed thyroid-stimulating hormone (TSH).[1] RTH was first reported by Refetoff in 1967,[2] which has been proved to be caused by mutation of the thyroid hormone receptor (TR) gene.[3-5] More than 3,000 cases have been reported.[6] About 80% of RTH is caused by *THRB* gene mutation, which is mainly autosomal dominant inheritance.[6] The clinical manifestations of RTH are extremely heterogeneous. Due to elevated thyroid hormone levels, it is often diagnosed as "hyperthyroidism" and treated with antithyroid drugs (ATD). In this article, we reported one Chinese pedigree with *THRB* gene mutation and reviewed the mutation characteristics of *THRB* gene in patients with RTH.

2 | CASE PRESENTATION

A 30-year-old female patient presented with palpitations. She had no heat intolerance, hyperhidrosis, or exophthalmos. The results of thyroid function test at a local hospital

were as follows: Free thyroxine (FT4) 26.65 pmol/L (12.00-22.00), Free triiodothyronine (FT3) 8.80 pmol/L (3.10-6.80), and TSH 4.70 mIU/L (0.27-4.20). She was diagnosed as "hyperthyroidism" and was treated with antithyroid drugs (propylthiouracil 150 mg/d for 1 week, then methimazole 10 mg/d for 2 weeks). After taking the medicine for 3 weeks, she presented FT4 15.35 pmol/L, FT3 5.58 pmol/L, and TSH 34.600 mIU/L. Then, she stopped taking the antithyroid drugs. Two weeks later, she was admitted to our hospital. The results of the thyroid function test (Chemiluminescent immunoassay, the Siemens ADVIA Centaur) were as follows: FT3 7.71 pmol/L (≥14 years old: 3.5-6.5, 2-14 years old: 5.1-7.4), FT4 24.67 pmol/L (≥14 years old: 11.5-22.7, 2-14 years old: 11.1-18.1), and TSH 6.891 mIU/L(≥ 12 years old: 0.55-4.78, <12 years old: 0.64-6.27).TSH receptor antibody (TRAb) and thyroid peroxidase antibody (TPOAb) were at 0.520 IU/L (0.00-1.75) and 402 IU/ml (0-35), respectively.

2.1 | Physical examination

The results of physical examination included: the height of 148 cm; the body weight of 40 kg; heart rate of 102 beats per min(bpm); and blood pressure of 120/83 mm Hg. Her thyroid gland was enlarged (degree I), but there was no exophthalmos and no myxedema in the lower extremities.

2.2 | Auxiliary examination

Somatostatin analog (Sandostatin, Novartis Pharma Schweiz AG. Switzerland, 0.1 mg, ih, once) inhibition test was conducted, and the result has shown that TSH could be inhibited to a maximum of 55.6% (Table 1). The result of bromocriptine (Novartis Pharma Schweiz AG. Switzerland, 2.5 mg, po, once) inhibition test showed that the maximum value of TSH inhibition was 68.4% (Table 1).

TABLE 1 Somatostatin analog (Sandostatin) and bromocriptine suppression tests

	Sandostatin			Bromocriptine
Time	FT4 (pmol/L)	FT3 (pmol/L)	TSH (mIU/L)	TSH(mIU/L)
0 h	24.30	7.56	6.047	12.012
2 h	24.84	7.60	3.524	6.084
4 h	21.28	6.79	3.133	5.042
6 h	20.22	6.46	2.692	3.858
8 h	19.95	6.18	2.686	3.801
24 h	22.16	6.46	5.610	5.610

Abbreviations: FT3, Free triiodothyronine; FT4, Free thyroxine;TSH, thyroid-stimulating hormone.

In an ultrasound examination, the Doppler signal of bilateral thyroid increased. Thyroid nuclide imaging showed slight enlargement of the thyroid gland on both sides and a slight increase of technetium uptake. Iodine uptake rate was 21.69% at 2 hours and 67.14% at 24 hours. Hearing examination indicated conductive deafness in the right ear. No abnormality was found in MRI contrast-enhanced scanning of the pituitary gland.

2.3 | Kindreds

The pedigree diagram and thyroid function of kindreds were shown in Figure 1 and Table 2, respectively. The proband's father (I1) died young, and her mother (I2) died in a car accident. Her brother's (II 1) height was 160 cm and had no clinical symptoms. The results of the brother's thyroid function assessment indicated that FT4 was at the upper limit of a normal reference value with normal level of TSH. The proband's sister (II 2) had no symptoms, either. The sister's height was 147 cm, and her thyroid gland was enlarged (degree II). The sister's thyroid function showed primary hypothyroidism combined with Hashimoto's thyroiditis. The sister has a 10-year-old son (III 1) and a 4-year-old daughter (III 2). They (III 1 and III 2) had normal intelligence and no clinical symptoms. The sister's son (III 1) was 136 cm tall (at the 10th percentile of the same sex and age in the same region) and had an enlarged thyroid gland (degree I), with elevated thyroid hormone level and inappropriate secretion of TSH. The sister's daughter (III 2) was 100 cm tall (at the 25th percentile of the same sex and age in the same region), with slightly increased FT4 accompanied by no inhibition of TSH. We did not know the details of the proband's younger brother (II 6, not in China). The proband has two sons (III 3 and III 4), who are twins of 10 years old. Their thyroid function showed that the high thyroid hormone level was accompanied by no inhibition of TSH. The first son (III 3) of the proband was diagnosed with rheumatoid arthritis at the age of 9 due to swelling and pain of the wrist joint of his right hand. Their heights were 129 cm (III 3, at the 3rd percentile of the same sex and age in the same region) and 127 cm (III4, lower than

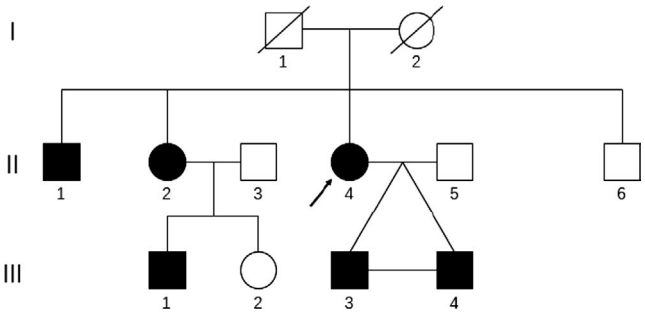

FIGURE 1 The pedigree of thyroid hormone resistance syndrome

TABLE 2 Thyroid hormone levels of the proband's kindred

	Sex	Age (y)	FT4 (pmol/L)	FT3 (pmol/L)	TSH (mIU/L)	TRAb (IU/L)	TPOAb (IU/mL)
II 1	Male	33	22.62	3.56	3.08	0.96	8.12
II 2	Female	31	7.13	3.23	>150	0.608	>1000
III 1	Male	9	32.03	9.66	5.896	<0.300	>1000
III 2	Female	4	18.67	6.11	1.853	<0.300	<10.0
III 3	Male	10	25.27	7.45	2.614	<0.300	<10.0
III 4	Male	10	29.44	8.35	3.001	<0.300	<10.0

Note: Normal Range: FT3, ≥14 y old: 3.5-6.5, 2-14 y old: 5.1-7.4. FT4, ≥14 y old: 11.5-22.7, 2-14 y old: 11.1-18.1. TSH, ≥12 y old: 0.55-4.78, <12 y old: 0.64-6.27. TRAb: 0.00-1.75. TPOAb: 0-35.

Abbreviations: FT3, Free triiodothyronine; FT4, Free thyroxine; TPOAb, thyroid peroxidase antibody; TRAb, TSH receptor antibody; TSH, thyroid-stimulating hormone.

the 3rd percentile of the same sex and age in the same area), respectively. Their (III3 and III 4) clinical manifestations included mental retardation, hyperactivity, inattention, and normal hearing.

2.4 | Gene detection

The Proband (II 4) had a mutation at exon10 c.G1378A of *THRB* gene as a missense mutation, and the encoded protein changed from glutamic acid to lysine (exon10 c.G1378A Heterozygous mutation, p.E460K) (Figure 2). Five kindreds (II 1, II 2, III 1, III 3, and III 4) shared the same mutation.

2.5 | Treatment and follow-up

The proband started bromocriptine 1.25 mg/d on July 23, 2018, and adjusted to the dose of 2.5 mg/d on January 3, 2019. After following up for more than 11 months, thyroid function test indicated that FT3 and FT4 did not change significantly. (Table 3).

3 | DISCUSSION

We report one Chinese pedigree of RTH caused by heterozygous mutation of *THRB* gene exon10c.G1378A. The clinical manifestations among family members are extremely heterogeneous.

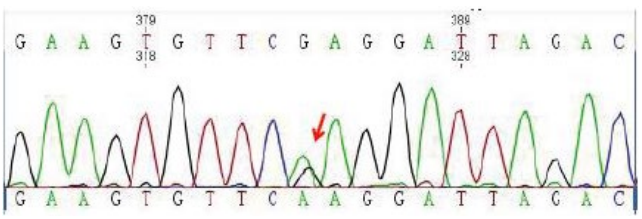

FIGURE 2 Partial sequencing result of exon 10 of the THRB gene. The arrow points to the base of *THRB* exon10:c. G1378A heterozygous missense mutation

The pedigree carried the *THRB* gene exon10 c.G1378A heterozygous missense mutation, which located in the hot spot mutation region. Adams M had reported the same mutation.[7] TR, which is a member of nuclear receptor superfamily, is composed of a single polypeptide chain and has three functional domains of module, including an amino-terminal domain, a central-DNA binding domain (DBD), and a carboxyl-terminal ligand-binding domain (LBD).[8] DBD interacts with specific sequences of DNA (thyroid hormone response element, TRE) to initiate transcription of target genes. LBD is combined with thyroid hormone. Normally, TR and retinoid X receptor (RXR) form heterodimers, which bind to TRE and corepressor to inhibit transcription of target genes. When thyroid hormone (T3) binds to TR, the corepressor is released and the coactivator is combined to promote transcription of the target gene.[9] When TR gene mutates, T3 cannot act on TR normally, resulting in RTH. The current reported RTH is mainly caused by *THRB* gene mutation. The *THRB* gene contains 10 exons, which encode 461 amino acids. A total of 172 *THRB* variants were identified.[10,11] The variations were almost located in exon 7-10,[10,11] which encoded three hot spots of LBD (aa 429-461, aa 309-383, aa 234-282 in amino acids 178-461).[12,13] These 172 variants consisted of substitution, duplication, deletion, and insertion. Among them, the most common variations were substitution, mostly missense mutation.[10,11] *THRB* gene mutation is mainly autosomal dominant inheritance. The patient has a mutant *THRB* allele expressing mutant TRβ (m TRβ) and a normal *THRB* allele expressing wild-type TRβ (wTRβ).[14] The mutant mTRβ, which has a dominant-negative effect, will inhibit the function of wTRβ. The mechanism of dominant-negative effect may be competitive inhibition of TREs and TR-auxiliary proteins (TRAPs), which lead to inhibit thyroid hormone regulation on target genes.[1]

The clinical heterogeneity of RTH caused by *THRB* gene mutation is extremely obvious, which is mainly due to the difference in tissue distribution of TR and response to

TABLE 3 Thyroid hormone levels of proband treated by bromocriptine

	FT4 (pmol/L)	FT3 (pmol/L)	TSH (mIU/L)
2018-7-13	24.30	7.56	6.047
2018-8-14	23.02	7.76	5.421
2018-11-5	21.92	6.88	5.798
2019-1-3	19.88	7.35	6.987
2019-7-24	22.04	6.85	6.283

elevated thyroid hormone. The same mutation can even lead to different clinical manifestations of RTH patients in the same family.[15] Thyromegaly is caused by stimulation of thyroid gland by inappropriate increase of TSH. Palpitations are caused by high levels of thyroid hormone stimulating TRα in the heart. Interestingly, the proband's elder sister carried the mutation of *THRB* gene exon10 c.G1378A, but her thyroid hormone level was decreased, while TSH and TPOAb were significantly increased. These are caused by RTH combined with Hashimoto's thyroiditis.[16] Children with RTH often have attention deficit hyperactivity disorder (ADHD).[17] RTH has a broad spectrum of clinical manifestations. Physicians need to identify these clinical manifestations of RTH to avoid misdiagnosis.

The thyroid function of RTH is characterized by elevated thyroid hormone level and unsuppressed TSH (normal or elevated TSH level), which is an important basis for diagnosis of RTH. It should be differentiated from Thyrotropin-secreting pituitary tumors.[18] The pituitary MRI of the proband showed normal, which was not consistent with Thyrotropin-secreting pituitary tumors. The thyroid function test of abnormalities of thyroid hormone transport in serum,[1] such as familial dysalbuminemic hyperthyroxinemia, hereditary and acquired thyroxine-binding globulin excess, and transthyretin excess is similar to RTH, but their FT4 is normal. Moreover, we should also consider the influence of immunoassay interference on thyroid function test results, but sometimes it is not easy to identify. Function test is helpful for identification. The core of RTH diagnosis is to prove that the response of tissues to thyroid hormone is decreased. T3 test is often used clinically (to observe the response of pituitary gland and tissues to T3 in the process of patients taking gradually increasing T3).[1] However, T3 is often unavailable in China. Theoretically, levothyroxine (L-T4) can also be used to examine the response of tissues to thyroid hormone. L-T4 takes effect slowly and needs to be able to transport into cells normally and generate T3 under the action of deiodinase (therefore, the results of L-4 test can also indicate whether there is abnormality in these two steps). In addition, at present, family history and gene detection are the confirmatory methods for diagnosing RTH. This is also the basis for diagnosing our patients as RTH. Reported genes causing RHT include *THRB*, *THRA*, *MCT8*, and *SBP2*, but there are still some patients with RTH who have not yet identified the mutated genes.[6] Therefore, we should comprehensively analyze the clinical manifestations, family history, thyroid function, tissue response to thyroid hormone, and gene detection of patient to improve the diagnosis of RTH.

As a monogenic disease, restoring the function of *THRB* gene is the fundamental treatment (such as gene therapy) for RTH. However, it is not clinically feasible at present and needs to wait for the technological development of gene therapy in the future. Treatment (such as ATD and radiotherapy) to reduce thyroid hormone should be avoided, so as not to significantly increase TSH and lead to pituitary hyperplasia or pituitary tumor.[19] For patients with clinical manifestations of hyperthyroidism, TSH-inhibiting drugs could be selected. Thyroid hormone analog 3,5,3′-Triiodothyroacetic Acid (TRIAC) is commonly used in clinical practice.[20] Compared with T3, TRIAC has an affinity for wTRβ of about 3.5 times, while its affinity for TRα is the same, and it degrades faster in vivo. TRIAC can increase the activation of wTRβ and reduce the dominant-negative effect of mTRβ without increasing the function of TRα, so TRIAC can inhibit TSH without increasing thyroid hormone-like effect. But TRIAC is not available in China. Somatostatin and dopamine receptor agonists can also inhibit TSH. For our patient (the proband), her pituitary response to somatostatin analog (Sandostatin) and bromocriptine showed that Sandostatin inhibited TSH at a maximum of 55.6% and bromocriptine inhibited TSH at a maximum of 68.4%. Sandostatin is a short-acting drug and needs injection therapy. It can inhibit TSH in a short time, but the long-term treatment effect is poor.[21] Therefore, she was treated with bromocriptine. After 11 months, her thyroid hormone level did not decrease significantly. In the further, we would confirm the adherence for bromocriptine administrations by detecting serum PRL levels. Also, we will gradually increase the dose of bromocriptine (up to 12.5 mg per day[22,23]). For the symptoms of hyperthyroidism, such as palpitations, beta adrenoreceptor blockers can be used. For patients with clinical manifestations of hypothyroidism or patients with Hashimoto's thyroiditis causing hypothyroidism (such as the proband's sister II2), hyperphysiological dose of thyroid hormone therapy is required.

There were some limitations in the present study. Firstly, we did not assess the circadian variations in the pedigree. Custro N reported that RTH has TSH rhythm which is similar to that of normal subjects, except for the persistently elevated 24 h levels.[24] Secondly, we did not carry out L-T4 test in our patients. Administration of L-T4 varied in dose (12.5-1000 μg/d) and duration (1 day to several years) in different studies.[1] It is necessary to establish the unified RTH confirmation test using L-T4. However, the *THRB* gene mutation in the pedigree confirmed the diagnosis of RTH.

In summary, we reported on the RTH pedigree in detail with clinical, laboratory, and genetic evaluations. The clinical manifestations of RTH are often atypical. Elevated thyroid hormone

level with unsuppressed TSH is an important feature of the disease. Family history and gene detection are the main basis for the diagnosis of RTH. It is important to make the correct diagnosis of RTH to avoid potential harmful treatment.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

The study concept and design were framed by ML and XL. BH and CL: collected the data and drafted the manuscript. FX, PH, JZ, and ZC: contributed to discussion and revision. All authors read and approved the final manuscript.

ETHICAL APPROVAL

Written informed consent for publication of this case report was obtained from the patient.

DATA AVAILABILITY STATEMENT

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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