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Resistance to thyroid hormone caused by a mutation of the thyroid β receptor gene in a family over three generations

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Resistance to thyroid hormone (RTH) is a rare condition, with an occurrence of one case per 40,000–50,000 live births. It was first described by Refetoff in 1967 and was linked to pathogenic variants resistant to thyroid hormone beta (RTHβ) in 1988 [1, 2]. Since then, more than 3000 cases from 1200 families worldwide have been reported, and a total of more than 170 THRB variants with pathogenic or unknown clinical significance have been identified [3, 4].

A 40-year-old male patient was first informed of his abnormal thyroid function one year earlier, during a routine physical examination. He experienced an increase of both free triiodothyronine (FT3) and free thyroxine (FT4), without any clinical manifestations (Tab. 1). In April 2019, symptoms of palpitation occurred. With the re-examination of abnormal thyroid function (FT3: 8.85 pmol/L, FT4: 33.34 pmol/L, TSH: 2.50 uIU/mL; Roche of Switzerland, thyroxine detection kit, electrochemical luminescence method), the patient was presumed to have primary hyperthyroidism. As a result, he was administered methimazole and propranolol under the advice of a local clinical practitioner. In June 2019, with weight loss of about 5 kg in the preceding few months, his third biochemical test showed an increase in both FT3 and FT4 with a normal TSH level. The patient was admitted to our hospital to seek further diagnosis and treatment in July 2019.

The father was in good health, and the mother had hyperthyroidism. Of the three elder sisters and one elder brother, the second sister suffered from hyperthyroidism.

On 2019.07.09, the following results were obtained: FT3 — 7.81 pmol/L, FT4 — 42.27 pmol/L, TSH — 4.2 uIU/mL. Magnetic resonance imaging (MRI) of pituitary gland: no abnormality observed. Thyroid ultrasound: multiple nodules in the left lobe of the thyroid, consistent with TI-RADS level 3. Electrocardiography (ECG) revealed sinus tachycardia.

The patient had symptoms and signs of hypermetabolism, but no obvious enlargement of the thyroid gland and normal TSH level were not consistent with the diagnosis of hyperthyroidism. The patient had senor nerve deafness and pituitary MRI results were normal. Meanwhile, many members of the family had been diagnosed with hyper-

Table 1. *Thyroid function tests of the propositus*

Variables/date	2018/7/26	2019/4/11	2019/6/26	2019/11/17	2020/8/8	Reference interval
FT3 [pmol/L]	10.59	8.85	12.11	5.86	7.80	3.1–6.8
FT4 [pmol/L]	50.67	33.34	54.38	10.32	62.59	12–22
TSH [uIU/mL]	2.771	2.5	1.501	> 50.00	1.94	0.27–4.2
TPO-Ab [IU/mL]	0.3	0.2	NA	0.1	NA	0–34
TG-Ab [IU/mL]	0.1	0.01	NA	0.01	NA	0–115

FT3 — free triiodothyronine; FT4 — free thyroxine; TSH — thyroid-stimulating hormone; TPO-Ab — thyroid peroxidase antibody; Tg-Ab — Tg antibody; NA — not available

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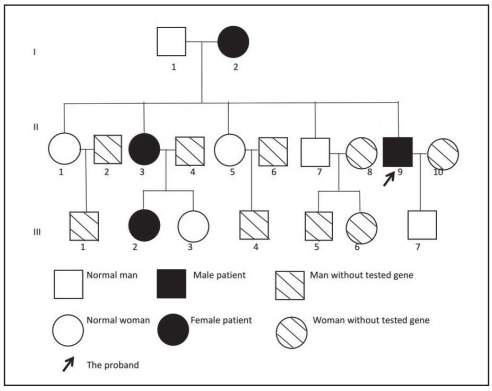

Figure 1. *Pedigree of family. Affected individuals (black symbols) were identified by elevated thyroid hormone levels and had genotypes characterised by mutation of C446S in the THR-b gene. Shaded symbols represent spouses that were not tested*

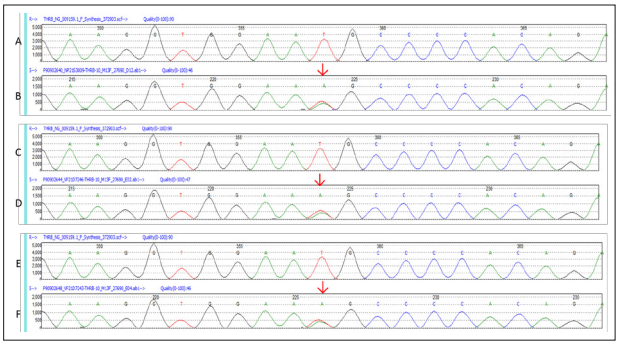

Figure 2. *The locus of the mutation. Note: A, C, and E are the same as the reference sequence. B, D, and F are the mutation sequence of the propositus, his mother, and his second sister, respectively (the mutated members of the family share the same mutation site, THRB 3p24.2 NM 000461.4 Exon10 c.1336T>A p.[Cys446Ser], heterozygosis).*

thyroidism. Therefore, the diagnosis of thyroid hormone resistance syndrome was considered. Dexamethasone inhibition test and genetic testing were carried out.

Genetic tests revealed a missense mutation in T1336A of exon 10 of the THRB gene. This was expected to replace cysteine with serine at amino acid number 446 of the protein encoded. After discharge from our hospital, the patient received controlled thyroid function treatment with propranolol (10 mg each time, 3 times a day) on the recommendation of his physician. One month later, his final thyroid function re-examination at the local hospital showed normal levels of both FT3 and FT4, but with a significant increase in his TSH level (Tab. 1).

After the patient was diagnosed with an abnormal thyroid function, his relatives also underwent genetic screening, and the same genetic mutation was found in his mother and second sister (Fig. 2). The propositus has a son and his second sister has two daughters. Among these three children, no clinical or genetic abnormalities were found except in the younger daughter of the patient's second sister. In this individual, a same missense mutation in T1336A of exon 10 of the THRB gene was detected, with high FT3 and FT4 levels, as well as a normal level of TSH (FT3 — 6.8 pmol/L; FT4 — 24.84 pmoL/L; TSH — 1.17 mIU/L).

We report a THRB gene mutation (C446S) in an individual combined with hyperthyroidism and taking antithyroid drugs with clinical and biochemical manifestations more severe than in the affected sibling and mother harbouring the same mutation. Although the first case of a C446S mutation in the THRB gene was reported in 2016, it lacked certain biochemical and genetic information about related family members, and paralysis is the main manifestation [5].

There is no clear guideline for the treatment of RTH. The first-line treatment is symptomatic treatment. The administration of antithyroid drugs is still controversial because TSH secretion is not reduced by antithyroid drug treatment. Conversely, a decrease in thyroid hormones stimulates the production of TSH, which in turn stimulates the formation of goitre. Other scholars believe that thyroid hormone is a compensatory mechanism, and the use of anti-thyroid drugs is not recommended [6]. In addition, tachycardia can be treated by the administration of β-blocker. Moreover, the application of 3, 3', 5-triiodothyroacetic acid (Triac) in RTH due to defective TRβ could be considered [7]. Furthermore, surgery or ablation is generally not an option because of the possibility of disruption of the pituitary-thyroid axis [8].

Authors' contributions

L.C. and L.D. contributed equally to this work and are co-first authors.

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