Thyroid hormone resistance syndrome due to a novel heterozygous mutation and concomitant Hashimoto’s Thyroiditis: A pedigree report

Zongyan Xie1, ChenFei Li2, Yaxin An2, Dong Zhao2 and Xuhong Wang1

Abstract
Thyroid hormone resistance syndrome (THRS) is a rare disease characterized by reduced sensitivity to thyroid hormones. Mutations in the thyroid hormone receptor beta (THRB) gene are considered as contributing to the pathogenesis. This report describes a Chinese pedigree with THRS and Hashimoto’s thyroiditis (HT) due to novel point mutation in the 11th exon of the THRB gene (c. 1378 G > A). The proband complained of goitre with increased thyroid hormone and normal thyroid stimulating hormone levels. Gene sequencing was performed to confirm the diagnosis. HT was also diagnosed based on positive thyroid autoantibodies and diffuse, grid-like changes in the thyroid on ultrasound examination. Additionally, a comprehensive examination of the proband’s pedigree was conducted. The patient’s father exhibited the same gene mutation site and was diagnosed with THRS and HT. No mutation site was detected in three patients with HT only and three healthy volunteers. Thus, gene sequencing should be considered the gold standard for diagnosing THRS. Furthermore, treatment should be individualized to control the patient’s symptoms rather than normalizing thyroid hormone levels. Further studies that determine the relationship between THRS and TH are warranted.

Keywords
Thyroid hormone resistance, gene mutation, Hashimoto’s thyroiditis

Date received: 4 May 2022; accepted: 6 June 2022

Corresponding author:
Professor Xuhong Wang, Department of Clinical Pharmacology, Beijing Luhe Hospital Affiliated to Capital Medical University, 82 Xinhua South Road, Beijing 101149, China.
Email: wangxuhong72@126.com
Introduction
Thyroid hormone resistance syndrome (THRS) is characterized by reduced sensitivity of target organs or tissues to thyroid hormones.\textsuperscript{1} The patient’s thyroid function is typically characterized by increased levels of circulating thyroid hormones, while the serum concentration of thyroid stimulating hormone (TSH) remains normal or slightly elevated.\textsuperscript{2,3} Most patients might simply exhibit elevated blood thyroid hormone levels with no obvious clinical manifestations.\textsuperscript{2,4} However, others potentially exhibit symptoms of hyperthyroidism, hypothyroidism or non-toxic goitre.\textsuperscript{4} It is a rare disease with an incidence of 1:40 000 to 1:50 000.\textsuperscript{5} This disease has a genetic predisposition, but a few cases are sporadic. The main cause of this disease is thyroid hormone receptor deficiency due to genetic mutations, which can be autosomal dominant or occasionally appear as recessive inheritance.\textsuperscript{5} Since resistance to thyroid hormones was initially observed in 1967,\textsuperscript{6} more than 1000 cases originating from over 370 families have been reported.\textsuperscript{7} Most cases (approximately 80–90\%) are caused by mutations in the thyroid hormone receptor beta (\textit{THRB}) gene on chromosome 3,\textsuperscript{7} while other cases are caused by mutations in the thyroid receptor \textit{x} gene located on chromosome 12 or genes related to the transport or metabolism of thyroid hormones.\textsuperscript{4} Research has demonstrated that the mutation sites of the \textit{THRB} gene are predominantly located on exons 7–10.\textsuperscript{8} This current case report presents a paediatric female patient with THRS harbouring a novel mutation site on exon 11 of the \textit{THRB} gene and concomitant Hashimoto’s thyroiditis (HT). The current literature on the relationship between \textit{THRB} and autoimmune thyroid disease has also been reviewed.

Case report
Proband
On 25 August 2017, the proband (III:1), a 10-year-old Chinese girl, was admitted to the Department of Endocrinology, Beijing Luhe Hospital Affiliated to Capital Medical University, Beijing, China, for goitre. Six months prior, she visited the doctor because her neck had thickened. Thyroid function tests were performed and the results were as follows: elevated total triiodothyronine (TT3, 2.59 ng/ml; normal range 0.61–1.77 ng/ml); elevated total thyroxine (TT4, 20.00 ug/dl; normal range 5.13–14.06 ug/dl); elevated free triiodothyronine (FT3, 6.55 pg/ml; normal range 2.02–4.33 pg/ml); elevated free thyroxine (FT4, 2.37 ng/dl; normal range 0.93–1.71 ng/dl); and a normal TSH level (4.0 \textmu{}IU/ml; normal range 0.27–4.2 \textmu{}IU/ml) (visit 1; Table 1). Thyroid autoantibody tests showed that the levels of thyroid peroxidase antibody (>1300 U/ml; normal range \leq 34 U/ml) and thyroglobulin antibody (248 U/ml; normal range \leq 115 U/ml) exceeded the normal range. No specific treatment was administered to the patient. Since then, the patient’s mother had observed a gradual enlargement of her daughter’s thyroid. Through careful medical history inquiry and comprehensive physical examination, this patient was found to have no clinical manifestations of hyperthyroidism or hypothyroidism, such as tachycardia or palpitations, heat intolerance, excessive sweating, fatigue, tremors, sensitivity to cold or unusual bowel habits. The patient’s body weight did not change significantly during the first half of the year. Additionally, the girl was born full-term, weighing 2.5 kg, with no history of radiation exposure or a family history of thyroid disease. Physical examination revealed the following: body...
temperature, 36.3 °C; pulse, 100 bpm; blood pressure, 105/70 mmHg; height, 138.6 cm; weight, 37.7 kg; normal development, vision, and hearing; a diffuse goitre with no palpable nodules, tenderness, tremor or vascular murmur; and no hand shaking or oedema in the lower extremities. A thyroid ultrasound revealed an enlarged thyroid volume and diffuse changes without thyroid nodules (left lobe, 3.9×1.4×1.2 cm; right lobe, 4.4×1.5×1.5 cm; isthmus, 0.3 cm). Thyroid echoes were neither even nor reticular. Routine blood and urine tests, blood glucose levels, blood lipid profiles and liver and kidney function were all within normal ranges. Gonadotropin hormone level was normal. The bone age was the same as the chronological age (Figure 1a). No occupying lesions were detected on the hypothalamic-pituitary magnetic resonance image (Figure 1b). Based on the clinical features and laboratory tests, THRS with concomitant HT was highly suspected in this patient. Gene sequencing was performed to confirm this hypothesis. Sequencing revealed a novel point mutation on the 11th exon of the \(THRB\) gene (c. 1378 G > A). This mutation causes the conversion of glutamic acid to lysine at position 460 (p. Glu460Lys). Thus, the patient was diagnosed with THRS based on genetic analysis and no medication was administered. After obtaining consent from her parents to treatment, 25 μg levothyroxine sodium was administered orally per day for 1.5 months to control goitre. During a follow-up visit (visit 2; Table 1), thyroid function was stable with no evidence of worsening thyrotoxicosis. There was no significant change in the goitre.

### Two kindreds

Patients with thyroid hormone resistance typically possess a family history of the disease. Therefore, the proband’s pedigree was comprehensively examined. Three generations of the pedigree are presented in Figure 1c. The proband’s grandmother had passed away and her parents had no siblings. The family exhibited no history of consanguineous marriages. Neither the proband’s parents nor grandfather had a history or symptoms of thyroid dysfunction. Thyroid function tests revealed that only the father (II:1) had an abnormal thyroid function. The results indicated increases in serum FT3, TT3 and FT4 levels, along with positive thyroid autoantibodies, while TSH levels remained normal (Table 2). Thyroid ultrasound examination revealed diffuse, grid-like changes in the proband’s father and normal changes in her mother and grandfather. Based on the same thyroid function, thyroid antibody, and thyroid ultrasound results as those of the proband, gene sequencing was

| Table 1. Thyroid function and thyroid autoantibody test results of the proband, a 10-year-old Chinese girl admitted for goitre. |
|-------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|
| FT3, pg/ml | FT4, ng/dl | TT3, ng/ml | TT4, μg/dl | TSH, μIU/ml | TPOAb, U/ml | TGAb, U/ml |
|----------------|---------|---------|---------|-----------|----------|----------|
| Visit 1 | 6.55 | 2.37 | 2.59 | 20.0 | 4.00 | >1300 | 248.0 |
| Visit 2 | 8.55 | 2.78 | 3.64 | 15.76 | 3.92 | 544.0 | 436.6 |
| Normal range | 2.02–4.33 | 0.93–1.71 | 0.61–1.77 | 5.13–14.06 | 0.27–4.2 | <34 | <115 |

FT3, free triiodothyronine; FT4, free thyroxine; TT3, total triiodothyronine; TT4, total thyroxine; TSH, thyroid stimulating hormone; TPOAb, thyroid peroxidase antibody; TGAb, thyroglobulin antibody.
performed on the father, with results revealing the same point mutation on the 11th exon of the \textit{THRB} gene (c. 1378 G > A) (Figure 1d). To rule out the possibility of this gene mutation appearing in patients with HT or in healthy individuals, gene sequencing was also performed on three patients with HT and three healthy volunteers; and no gene mutations were detected.

This study was approved by the Ethics Committee of Capital Medical University, affiliated with Beijing Luhe Hospital (no. 2016-L-H-KS-08[ST]). Verbal informed consent was obtained from all study participants for publication of this report. The reporting of this case and family pedigree conforms to the CARE guidelines.9

**Discussion**

Thyroid hormone resistance syndrome is a disorder characterized by a suppressed response to thyroid hormones due to mutations in the thyroid hormone receptor
There are two subtypes of human thyroid hormone receptors: THRα and THRβ. Each subtype has different isoforms, such as THRα1, THRα2, THRβ1, THRβ2 and THRβ3. These receptors possess specific organ distribution characteristics. Additionally, genetic defects involving TH cell transport and metabolism have been reported, broadening the understanding of impaired TH sensitivity. All these features determine the diversity of the clinical manifestations of THRS. Based on clinical manifestations, THRS can be divided into the following three categories: global resistance (GRTH), pituitary resistance (PRTH) and peripheral resistance (PrRTH) to thyroid hormones. GRTH, which affects the majority of patients, has no distinctive manifestations, except for goitre. Patients with PRTH predominantly experience mild-to-moderate hyperthyroidism without ophthalmopathy or pretibial myxoedema. PRTH potentially causes symptoms or signs of hypothyroidism. The multiplicity of symptoms without a typical model renders it difficult to diagnose this disease. To date, gene sequencing is considered the gold standard for diagnosing THRS.

To date, numerous mutations have been identified. Of these mutations, 85% are located in the THRB gene, which comprises 10 exons. Most studies on THRB gene mutations have revealed that these mutations often occur in three hotspot regions between exons 7 and 10, that is, codons 234–282, 310–353 and 429–461. Only a few cases have presented mutation sites at codons 384–425, which constitutes the ‘cold region’. Point mutations are prevalent, causing missense mutations, while insertion and deletion mutations are relatively rare. In this current report, the proband exhibited no distinctive manifestations, except for goitre. Thyroid function tests revealed increased levels of circulating thyroid hormones, with normal TSH concentrations. Gene sequencing revealed a novel point mutation on the 11th exon of the THRB gene (c. 1378 G > A). A comprehensive examination of the proband’s pedigree was conducted and the patient’s father was found to have the same thyroid function and gene mutation site. Thus, the patient’s father was diagnosed with THRS due to a new point mutation on the 11th exon of the THRB gene (c. 1378 G > A).

In this current pedigree report, both the proband and her father were found to be positive for thyroglobulin and thyroid peroxidase antibodies. In early 2008, a causal link between thyroid hormone resistance and primary autoimmune hypothyroidism was proposed. The authors claimed that chronic TSH elevation in thyroid hormone resistance stimulates lymphocytes to produce the proinflammatory cytokine tumour necrosis factor-α, which mediates thyroid cell destruction by binding to its receptors on thyrocytes, or indirectly, by potentiating antibody formation. Increased thyroid hormones may promote a high inflammatory burden. In contrast, HT is considered to be an autoimmune inflammatory disorder, which has been linked with inflammation. Thus, the inflammation might explain the coincidence of THRS and HT. Although the diagnosis of HT in patients with THRS has been reported in a number of cases, whether HT is more prevalent in THRS or whether it merely coexists in the same individual by coincidence remains debatable. Current research has demonstrated that both HT and THRS exhibit certain genetic tendencies. Considering the above theory and this current pedigree report, we believe that THRS increases the risk of HT. Thus, in the future,
focus should be directed on the incidence of HT in patients with THRS. In addition, its pathogenesis needs to be determined.

In conclusion, THRS has no specific clinical features. Most patients with THRS exhibit normal growth and present only with goitre and high TH levels, rendering the diagnosis of this disease difficult. Gene sequencing is considered the gold standard for diagnosing THRS. Furthermore, treatment should be individualized to control the patient’s symptoms rather than normalizing elevated TH levels. The advances in our knowledge about THRS raise novel questions regarding the susceptibility of patients with THRS to TH. Further studies that explore the relationship between these two diseases in terms of molecular and genetic pathogenesis are warranted.

Author contributions
Z.Y.X. and X.H.W. designed the study. C.F.L. and Y.X.A. collected the data. Z.Y.X. analysed the data and wrote the case report. D.Z. and X.H.W. contributed to the discussion of the results and review of the manuscript. All authors read and approved the final manuscript.

Declaration of conflicting interest
The authors declare that there are no conflicts of interest.

Funding
This research received no specific grant from funding agency in the public, commercial, or not-for-profit sectors.

ORCID iDs
Zongyan Xie https://orcid.org/0000-0002-7372-2501
Dong Zhao https://orcid.org/0000-0002-9847-5439

References
1. Chatterjee VK. Resistance to thyroid hormone. Horm Res 1997; 48 Suppl 4: 43–46. 1997/01/01. DOI: 10.1159/000191312.
2. Agrawal NK, Goyal R, Rastogi A, et al. Thyroid hormone resistance. Postgrad Med J 2008; 84: 473–477. 2008/10/23. DOI: 10.1136/pgmj.2008.069740.
3. Pappa T and Refetoff S. Resistance to Thyroid Hormone Beta: A Focused Review. Front Endocrinol (Lausanne) 2021; 12: 656551. 2021/04/20. DOI: 10.3389/fendo.2021.656551.
4. Onigata K and Szinnai G. Resistance to thyroid hormone. Endocr Dev 2014; 26: 118–129. 2014/09/19. DOI: 10.1159/000363159.
5. Sun H, Cao L, Zheng R, et al. Update on resistance to thyroid hormone syndrome-beta. Ital J Pediatr 2020; 46: 168. 2020/11/13. DOI: 10.1186/s13052-020-00929-x.
6. Refetoff S, DeWind LT and DeGroot LJ. Familial syndrome combining deaf-mutism, stippled epiphyses, goiter and abnormally high PBI: possible target organ refractoriness to thyroid hormone. J Clin Endocrinol Metab 1967; 27: 279–294. 1967/02/01. DOI: 10.1210/jcem-27-2-279.
7. Teng X, Jin T, Brent GA, et al. A Patient With a Thyrotropin-Secreting Microadenoma and Resistance to Thyroid Hormone (P453T). J Clin Endocrinol Metab 2015; 100: 2511–2514. 2015/04/14. DOI: 10.1210/jc.2014-3994.
8. Concolino P, Costella A and Paragliola RM. Mutational Landscape of Resistance to Thyroid Hormone Beta (RTHbeta). Mol Diagn Ther 2019; 23: 353–368. 2019/04/13. DOI: 10.1007/s40291-019-00399-w.
9. Gagnier JJ, Kienle G, Altman DG, et al. The CARE guidelines: consensus-based clinical case reporting guideline development. Headache 2013;53: 1541–1547. DOI: 10.1111/head.12246.
10. van Gucht ALM, Moran C, Meima ME, et al. Resistance to Thyroid Hormone due to Heterozygous Mutations in Thyroid Hormone Receptor Alpha. Curr Top Dev Biol 2017; 125: 337–355. 2017/05/22. DOI: 10.1016/bs.ctdb.2017.02.001.
11. Pappa T and Refetoff S. Human Genetics of Thyroid Hormone Receptor Beta: Resistance to Thyroid Hormone Beta (RTHbeta). Methods Mol Biol 2018; 1801: 225–240. 2018/06/13. DOI: 10.1007/978-1-4939-7902-8_18.
12. Liang Y, Zhao D, Wang R, et al. Generation and Characterization of a New Resistance to Thyroid Hormone Mouse Model with Thyroid Hormone Receptor Alpha Gene Mutation. *Thyroid* 2021; 31: 678–691. 2020/09/15. DOI: 10.1089/thy.2019.0733.

13. Wang J and Lv H. Identification of a novel mutation in the thyroid hormone receptor beta gene that causes thyroid hormone resistance syndrome: A case report. *Mol Med Rep* 2019; 20: 4683–4687. 2019/11/09. DOI: 10.3892/mmr.2019.10703.

14. Yu C, Zhao J, Yao J, et al. Pituitary resistance to thyroid hormone caused by a novel mutation (H435A) in the thyroid hormone receptor beta gene: A case report. *Medicine (Baltimore)* 2018; 97: e10544. 2018/05/26. DOI: 10.1097/MD.0000000000010544.

15. Ito J, Narumi S, Nishizawa K, et al. A novel mutation of the THRB gene in a Japanese family with resistance to thyroid hormone. *Clin Pediatr Endocrinol* 2016; 25: 19–22. 2016/02/13. DOI: 10.1297/cpe.25.19.

16. Guo QH, Wang BA, Wang CZ, et al. Thyroid hormone resistance syndrome caused by heterozygous A317T mutation in thyroid hormone receptor beta gene: Report of one Chinese pedigree and review of the literature. *Medicine (Baltimore)* 2016; 95: e4415. 2016/08/19. DOI: 10.1097/MD.0000000000004415.

17. Korwutthikulrangsri M, Dosiou C, Dumitrescu AM, et al. A Novel G385E Variant in the Cold Region of the T3-Binding Domain of Thyroid Hormone Receptor Beta Gene and Investigations to Assess Its Clinical Significance. *Eur Thyroid J* 2019; 8: 293–297. 2020/01/15. DOI: 10.1159/000503860.

18. Gavin C, Meggison H and Ooi TC. Proposing a causal link between thyroid hormone resistance and primary autoimmune hypothyroidism. *Med Hypotheses* 2008; 70: 1024–1028. 2007/10/09. DOI: 10.1016/j.mehy.2007.08.015.

19. Franklyn JA and Boelaert K. Thyrotoxicosis. *Lancet* 2012; 379: 1155–1166. 2012/03/08. DOI: 10.1016/S0140-6736(11)60782-4.

20. Aktas G, Sit M, Dikbas O, et al. Elevated neutrophil-to-lymphocyte ratio in the diagnosis of Hashimoto’s thyroiditis. *Rev Assoc Med Bras (1992)* 2017; 63: 1065–1068. 2018/03/01. DOI: 10.1590/1806-9282.63.12.1065.

21. Aktas G, Sit M, Dikbas O, et al. Could red cell distribution width be a marker in Hashimoto’s thyroiditis? *Exp Clin Endocrinol Diabetes* 2014; 122: 572–574. 2014/11/08. DOI: 10.1055/s-0034-1383564.

22. Kurtkulagi O, Tel BMA, Kahveci G, et al. Hashimoto’s thyroiditis is associated with elevated serum uric acid to high density lipoprotein-cholesterol ratio. *Rom J Intern Med* 2021; 59: 403–408. 2021/06/19. DOI: 10.2478/rjim-2021-0023.

23. Sato H and Sakai H. A family showing resistance to thyroid hormone associated with chronic thyroiditis and its clinical features: A case report. *Endocr J* 2006; 53: 421–425. 2006/05/26. DOI: 10.1507/endocrj.k05-182.

24. Savovska M, Stojanoski S and Manevska N. A Rare Case of Partial Peripheral Thyroid Hormone Resistance Due to a Point Mutation in the Membrane Integrin Alpha (V)Beta(3) and Concomitant Hashimoto’s Thyroiditis. *Open Access Maced J Med Sci* 2019; 7: 1991–1997. 2019/08/14. DOI: 10.3889/oamjms.2019.582.

25. Barkoff MS, Koehrigsky M, Anselmo J, et al. Autoimmunity in patients with resistance to thyroid hormone. *J Clin Endocrinol Metab* 2010; 95: 3189–3193. 2010/05/07. DOI: 10.1210/jc.2009-2179.

26. Lamberg BA, Rosengard S, Liewendahl K, et al. Familial partial peripheral resistance to thyroid hormones. *Acta Endocrinol (Copenh)* 1978; 87: 303–312. 1978/02/01. DOI: 10.1530/acta.0.0870303.

27. Ralli M, Angeletti D, Fiore M, et al. Hashimoto’s thyroiditis: An update on pathogenic mechanisms, diagnostic protocols, therapeutic strategies, and potential malignant transformation. *Autoimmun Rev* 2020; 19: 102649. 20200815. DOI: 10.1016/j.autrev.2020.102649.