Annals of Clinical Case Reports

Research Article
Published: 25 Nov, 2022

Thyroid Hormone Resistance Syndrome Caused by Heterozygous R338W Mutation in Thyroid Hormone Receptor β: Report of one Chinese Pedigree a in Southwest China

*Tang K[1#], Zhuang H[1#], Liu R[1], Chen Z[1] and Li H[1,2]**

[1]Department of Endocrinology, The Affiliated Hospital of Guizhou Medical University, Guiyang, China

[2]Shanghai Jiao Tong University School of Medicine, Shanghai, China

[#]These authors contributed equally to this work

Abstract

A clinical investigation was conducted on a family of 10 members with thyroid hormone resistance syndrome, including the proband, and gene sequencing analysis was performed. The proband in this family has symptoms of hyperthyroidism such as heart palpitations, fear of heat, and hyperhidrosis. Genetic testing revealed a missense mutation in the 1012[th] base of exon 9 of the patient's THRβ gene from cytosine to thymine T, which resulted in a change in amino acid 338 from arginine to tryptophan (R338W). The patient's mother also had the same mutation, but other relatives of the patient did not find this mutation. This mutation is heterozygous and may lead to the synthesis of thyroid hormone resistance.

Keywords: Thyroid hormone resistance syndrome; Thyroid hormone receptor beta gene mutation; gene sequencing analysis

OPEN ACCESS

Correspondence:
Hong Li, Department of Endocrinology, The Affiliated Hospital of Guizhou Medical University, Guiyang, China, Fax: +86-851-86770523; Tel: +8618621570466; E-mail: lee-helen@sjtu.edu.cn

Received Date: *07 Nov 2022*
Accepted Date: *21 Nov 2022*
Published Date: *25 Nov 2022*

Citation:
Tang K, Zhuang H, Liu R, Chen Z, Li H. Thyroid Hormone Resistance Syndrome Caused by Heterozygous R338W Mutation in Thyroid Hormone Receptor β: Report of one Chinese Pedigree a in Southwest China. Ann Clin Case Rep. 2022; 7: 2355.
ISSN: 2474-1655.

Introduction

Thyroid hormone Resistance syndrome (RTH) is a disease characterized by decreased responsiveness of target tissues (pituitary gland and/or surrounding tissues) to thyroid hormones [1,2]. This may be caused by mutations in the Thyroid Hormone Receptor (THR) gene. It is a rare autosomal dominant or recessive disease that occurs in families or sporadic cases, which an incidence is about 1:40000-50000 [3,4]. To date, over 100 mutations, more than 3,000 cases have been published [5-7]. The clinical characteristics of RTH are diverse and manifest in many ways, including hyperthyroidism, hypothyroidism, and non-toxic goiter. However, it is a common clinical feature that blood thyroid hormone levels are not suppressed [8].

According to the different subtypes of mutant receptors, RTH could be divided into thyroid hormone receptor α gene mutation-induced RTH (RTHα) and thyroid hormone receptor β gene mutation-induced RTH (RTHβ). In total, 85% of RTH cases are caused by mutations in the THRβ gene. Gene sequencing is the gold standard for diagnosing RTH. More than 300 families and 1,000 case reports have been reported since the Refetoff group first reported RTH in 1967 [9]. This study conducted genetic mutation detection on a case of thyroid hormone resistance syndrome and its family, combined with clinical data, aimed at understanding the pathogenesis of the disease at the molecular level, and providing a practical basis for clinical diagnosis and effective treatment at the genetic level. Although there have been reports of R338W mutations in other cities of China, it is the first time in Guizhou.

Clinical Data

Proband

A 26-years-old male came for diagnosis of palpitations, irritability, hunger, hyperphagia, fear of heat, hyperhidrosis, accompanied by insomnia, fatigue, headache, and weight loss of about 3 kg without obvious inducement for 1 year. The proband visited the hospital to check and previous thyroid function showed that Serum Free Triiodothyronine (FT3) 12.7 pmol/L (reference values: 0.66-1.92), Serum Free Thyroxine (FT4) 58.1 pmol/L (reference values: 0.66-1.92), and Thyroid

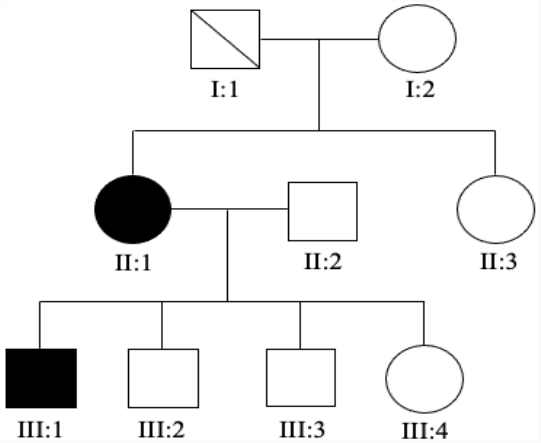

Figure 1: Family diagram of RTH patients.

Stimulating Hormone (TSH) values were normal. In his history, the proband was born full-term, he has normal growth and development in his childhood, but he has poor academic performance. In addition, he has normal development of secondary sexual characteristics and no hearing impairment. His family history showed his mother's thyroid function test revealed FT3 7.99 pmol/L, FT4 34.22 pmol/L, TSH 2.9 nmol/L; and his aunt suffers from "hyperthyroidism", currently taking "Methimazole 5 mg once a day" for treatment. Physical examination includes height 168 cm; weight 55 kg; BMI 19.5 kg/m^2; waist 68 cm; blood pressure 110/70 mmHg; normal development, medium nutrition, damp skin, negative eye symptoms; thyroid enlargement (degree II), soft and no nodules, no tenderness, tremor or vascular murmur; heart rate 106 beats/min, no arrhythmias; no hands shaking; no edema in lower extremities. The thyroid function was checked twice during the period, and the results were FT3 14.94 pmol/L to 13.24 pmol/L (reference 3.1-6.8), FT4 70.2 pmol/L to 53.46 pmol/L (reference 12.0-22.0), TSH 4.2 mU/L to 3.44 mU/L (reference 0.27-4.2). Other laboratory findings include: Thyroglobulin Antibody (TGAb) <10 (reference 0-115), Thyroid Peroxidase Antibody (TPOAb) 12.17 U/ml (reference 0-34), Thyrotropin Receptor Antibody (TRAb) <0.3 U/ml (reference 0-1.75). Sex hormone-binding globulin 16.5 nmol/L (reference 13-71). The results of Follicle-Stimulating Hormone (FSH), Luteinizing Hormone (LH), estradiol, testosterone, progesterone, prolactin (PRL), Growth Hormone (GH), Insulin Growth Factor-1 (IGF-1), cortisol (8:00), ACTH (8:00) complete blood count, routine urinalysis, blood glucose, and renal function were all within normal ranges. Thyroid ultrasound showed multiple cystic nodules in the bilateral lobes of the thyroid, which was classified into 2 categories by TI-RADS. MRI scanning of the pituitary gland displayed no abnormalities in the sellar area. To sum up, it is considered the diagnosis of thyroid hormone resistance syndrome (pituitary type).

Kindreds

Three generations of the pedigree are presented in Figure 1. The family had no history of consanguineous marriage. The proband (III:1) had two younger brothers (III:2, III:3) and a sister (III:4) with no history and symptoms of hyperthyroidism. The proband's mother (II:2) had thyroid disease, but the details are not clear. The thyroid function results of the outside hospital indicate that FT3 and FT4 are both increased, and TSH is normal at the same time. His aunt was diagnosed with "hyperthyroidism" in the outer hospital and has been treated with antithyroid drugs.

Methods

Extraction of genomic DNA from peripheral blood

Venous blood (5 mL) was drawn from the proband and his kindreds, centrifuged at 3000 rpm for 7 min, and separated white blood cells. Peripheral blood leukocyte DNA was extracted according to the standard phenol-chloroform method. The purity and concentration of each DNA sample were determined by a UV spectrophotometer.

Amplification and sequencing of THRβ gene

High-throughput sequencing and Sanger verification are used for detection. The primer synthesis, PCR reaction, and sequencing process were all completed by MyGenostic company (Beijing).

Results

We sequenced the THRβ gene for the proband and found a heterozygous C>T missense mutation at nucleotide position 1012 in Exon 9, which changed the trinucleotide codon and led to a transition from Arginine to Tryptophan at position 338 of the gene-coding product. We also sequenced Exon 9 for the other kindreds and found that the proband's mother shared the same mutation, whereas the rest of the family did not harbor it (Figure 2).

Discussion

Thyroid hormone resistance syndrome is a rare genetic disease, inherited in an autosomal dominant or recessive manner, with elevated levels of Free Triiodothyronine (FT3) and serum-Free Thyroxine (FT4), accompanied by stimulating Unsuppressed elevated or normal thyroxine (TSH) is the basic feature [10,11]. According to the distribution of tissues that are not sensitive to thyroid hormones, it can be divided into systemic hormone resistance, pituitary sex hormone resistance, and peripheral sex hormone resistance. About 80% of the cases belong to pituitary hormone resistance.

THRα and β have the function of encoding thyroid hormone receptors, and their mutations could cause a decrease in the affinity of triiodothyronine and the receptor, which results in a decrease in transcriptional activity and a compensatory increase in thyroid hormones, which ultimately causing thyroid hormone resistance syndrome. At present, there have been many reports on the two forms of gene mutations, it seems that different mutation forms can lead to different clinical phenotypes [12,13]. 85% of RTH is caused by mutations in the gene encoding THRβ in clinical practice, which

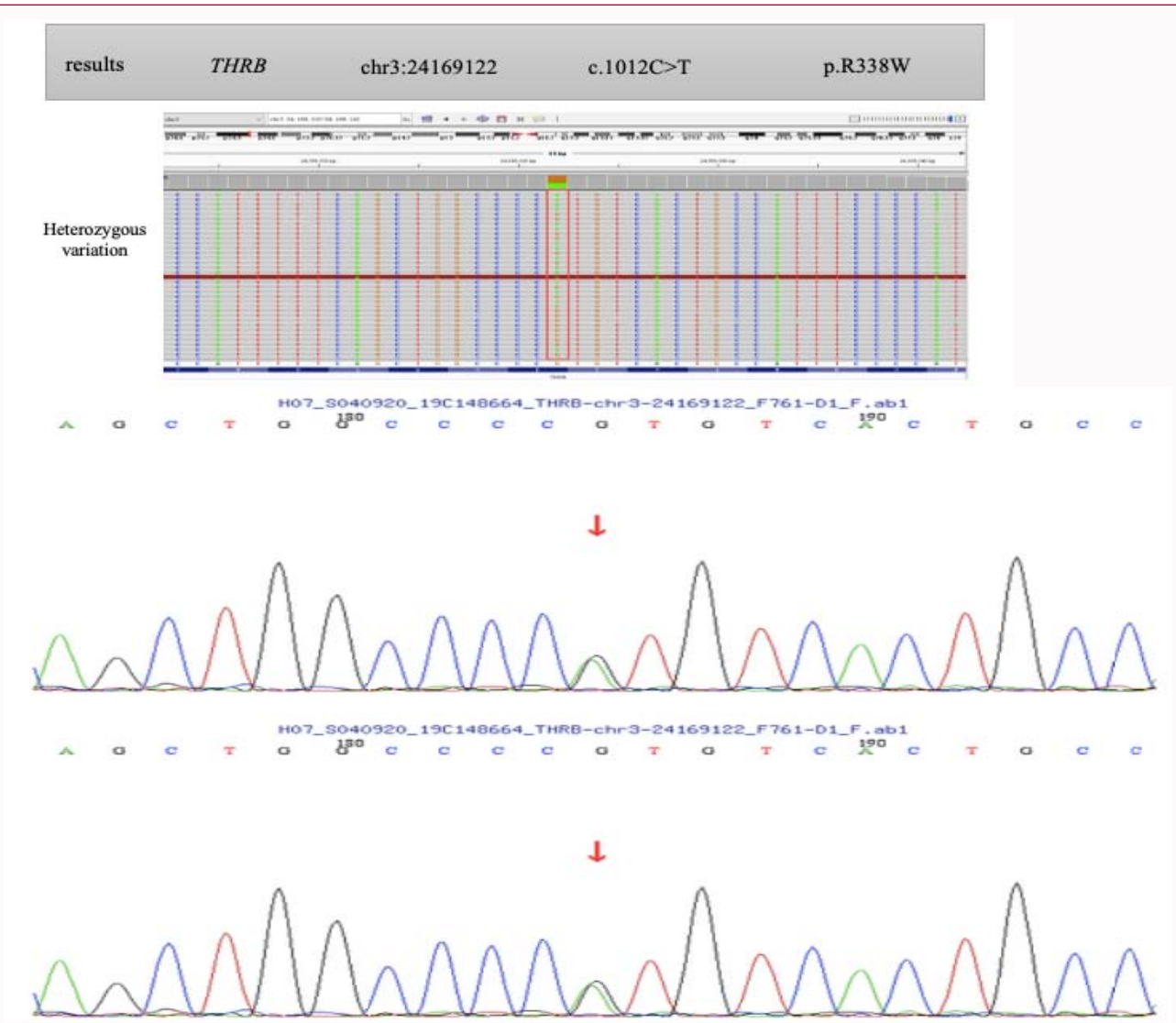

Figure 2: Results of genetic testing (The arrow points to the mutation point).

is considered to be the most important cause of RTH [14]. The THRβ gene includes 10 exons, of which the 7-10th exons encode amino acids 178-461 which constitute the ligand-binding domain and part of the hinge region at the carboxyl end of THRβ that bind to ligands and co-modulators. The hotspot mutation regions rich in CG sequences are concentrated here [15]. Although most of the patients are heterozygous, but also case reports of homozygous mutations [16].

The proband in this family is a 26-year-old male with typical clinical manifestations of hyperthyroidism such as palpitations, irritability, hunger, polyphagia, heat tolerance, and sweating, without exophthalmos and anterior tibial mucoedema. Multiple thyroid functions showed that FT3 and FT4 are higher and TSH level is in the normal range, which could exclude hyperthyroidism caused by thyroid function. In addition, the pituitary gland scan of MRI showed no abnormality. The patient's mother also had similar thyroid hormone results. Meanwhile, his aunt had been diagnosed with hyperthyroidism that was treated with medication. To sum up, it is considered that the patient may have pituitary thyroid resistance syndrome. In addition, gene sequencing analysis revealed that both the proband and his mother had heterozygous missense point mutation R338W in exon 9 of the THRβ gene, while other members of the family had neither clinical symptom of hyperthyroidism nor mutations in the THRβ gene. It is further confirmed that the patient meets the diagnosis of thyroid hormone resistance syndrome.

R338W is one of the hotspot mutations reported in western countries so far. The following R338W, A317T, R438H, R243Q, and P453T are the five most reported mutation sites abroad, respectively [17,18]. The mutation sites reported so far in China are P453A, H435L, V458A, P453S, A317T, I1276L and so on [19-23].

At present, two cases of R338W mutant thyroid hormone resistance syndrome have been reported in China [24], one case is Generalized Resistance to Thyroid Hormone (GRTH) and another is Pituitary Resistance to Thyroid Hormone (PRTH). Both patients were female and both were diagnosed in adolescence. Although they all have goiters, the clinical manifestations are not the same. One patient mainly showed hyperactivity and learning disabilities, and the other mainly showed heart palpitations and weight loss. But the male patient we reported onset in adulthood, not only has a goiter, but also has palpitations, irritability, hunger, polyphagia, fear of heat, hyperhidrosis, insomnia, fatigue, headache, weight loss symptoms, and poor performance. After genetic testing revealed that all these

three cases had heterozygous missense point mutation R338W in exon 9 of the THRβ gene, which led to a transition from Arginine to Tryptophan at position 338 of the gene-coding product.

Qian Yanying et al. searched the literature published in China from 1989 to 2017, retrospectively analyzed the family characteristics of thyroid hormone resistance syndrome caused by mutation of thyroid hormone receptor β gene, and found that adults often seek medical treatment due to thyrotoxicosis-related symptoms or the discovery of thyroid enlargement, while children due to hyperactivity and learning disabilities, and some patients may be asymptomatic [23]. It is showed that the clinical manifestations of the disease are heterogeneous, and this feature is similar to that of our family. The proband of this family has second-degree thyroid intumescence, but his mother has no such clinical manifestations. Different members of the same family could have different clinical manifestations even if the mutation site is the same, which may be due to differences in receptor expression and function among different individuals [25]. In addition, it has also been reported that the same gene locus mutation could also lead to resistance of different phenotypes, which may be related to the distribution of receptors [22].

Currently, there is no radical treatment for RTH, and it needs to be judged based on symptoms. Most patients could increase endogenous thyroid hormones to compensate for the resistance of tissues and organs. Generally, treatment is not required because inappropriate drug intervention may break the balance. When there is obvious tachycardia, beta-blockers could be considered to combat the tachycardia caused by hyperthyroidism.

In summary, the current pathogenic mechanism of RTH is not yet clear, and the clinical manifestations are not specific. It is easy to be missed and misdiagnosed. THRβ gene detection plays an important role in the diagnosis which is used for suspected thyroid hormone resistance syndrome patients and their close relatives. Detection could confirm the diagnosis as soon as possible and reduce the occurrence of adverse outcomes.

Acknowledgment

Kun Tang contributes to analysis and draft the article; Huijun Zhuang contributes to interpretate data and modify articles; Hong Li contributes to design the whole work and approve the final version.

Funding

This work was supported by grants from the National Key R&D Program of China (2017YFC1310704).

References

1. Refetoff S, Bassett JHD, Beck-Peccoz P, Bernal J, Brent G, Chatterjee K, et al. Classification and proposed nomenclature for inherited defects of thyroid hormone action, cell transport, and metabolism. Eur Thyroid J. 2014;3(1):7-9.
2. Pappa T, Anselmo J, Mamanasiri S, Dumitrescu AM, Weiss RE, Refetoff S. Prenatal diagnosis of resistance to thyroid hormone and its clinical implications. J Clin Endocrinol Metab. 2017;102(10):3775-82.
3. Pohlenz J, Weiss RE, Macchia PE, Pannain S, Lau IT, Ho H, et al. Five new families with resistance to thyroid hormone not caused by mutations in the thyroid hormone receptor beta gene. J Clin Endocrinol Metab. 1999;84(11):3919-28.
4. Weiss RE, Balzano S, Scherberg NH, Refetoff S. Neonatal detection of generalized resistance to thyroid hormone. JAMA. 1990;264(17):2245-50.
5. Persani L, Campi I. Syndromes of resistance to thyroid hormone action. Exp Suppl. 2019;111:55-84.
6. Beck-Peccoz P, Chatterjee VK, Chin WW, DeGroot LJ, Jameson JL, Nakamura H, et al. 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. 1994;78(4):990-3.
7. Dumitrescu AM, Refetoff S. The syndromes of reduced sensitivity to thyroid hormone. Biochim Biophys Acta. 2013;1830(7):3987-4003.
8. Cheng SY, Leonard JL, Davis PJ. Molecular aspects of thyroid hormone actions. Endocr Rev. 2010;31(2):139-70.
9. Refetoff S, Dewind LT, 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(2):279-94.
10. Vela A, Pérez-Nanclares G, Ríos I, Rica I, Portillo N, Castaño L, et al. Thyroid hormone resistance from newborns to adults: A Spanish experience. J Endocrinol Invest. 2019;42(8):941-9.
11. Agrawal NK, Goyal R, Rastogi A. Thyroid hormone resistance. Postgrad Med J. 2008;84(995):473-7.
12. Bochukova E, Schoenmakers N, Agostini M, Schoenmakers E, Rajanayagam O, Keogh JM, et al. A mutation in the thyroid hormone receptor alpha gene. N Engl J Med. 2011;366:243-9.
13. Mamanasiri S, Yesil S, Dumitrescu AM, Liao XH, Demir T, Weiss RE, et al. Mosaicism of a thyroid hormone receptor-beta gene mutation in resistance to thyroid hormone. J Clin Endocrinol Metab. 2006;91(9):3471-7.
14. Nagaya T, Seo H. Molecular basis of resistance to thyroid hormone (RTH). Endocr J. 1998;45(6):709-18.
15. Owen PJ, Chatterjee VK, John R. Augmentation index in resistance to thyroid hormone (RTH). Clin Endocrinol. 2010;70(4):650-54.
16. Ferrara AM, Onigata K, Ercan O, Woodhead H, Weiss RE, Refetoff S. Homozygous thyroid hormone receptor β-gene mutations in resistance to thyroid hormone: Three new cases and review of the literature. J Clin Endocrinol Metab. 2012(4):1328-36.
17. Refetoff S. Resistance to thyroid hormone with and without receptor gene mutations. Ann Endocrinol (Paris). 2003;64(1):23-5.
18. Boothroyd CV, Teh BT, Hayward NK, Hickman PE, Ward GJ, Cameron DP. Single base mutation in the hormone binding domain of the thyroid hormone receptor beta gene in generalised thyroid hormone resistance demonstrated by single stranded conformation polymorphism analysis. Biochem Biophys Res Commun. 1991;178(2):606-612.
19. Jing-fang L, Bingyin S. Study on TRβ gene mutation in a thyroid hormone resistance syndrome family. Chin J Med Genet. 2006;23(4):423-6.
20. Xiaolan L, Min N, Yao B. Thyroid hormone resistance with H435L mutation in exon 10 of thyroid hormone receptor β gene associated with Hashimoto's thyroiditis. Basic Clin Med. 2009;29(9):974-8.
21. Fang Y, YongJu Z, Ying C. Thyroid hormone resistance syndrome caused by V458A mutation in the thyroid hormone receptor β gene. Chin J Endocrinol Metabol. 2004;020(004):311-3.
22. Baoan W, Min W, Juming L. Pedigree analysis of a pituitary-resistance to thyroid hormone syndrome family caused by heterozygous A317T mutation in thyroid hormone receptor β gene. Chin J Endocrinol Metabol. 2017;33(3):215-9.
23. Yanying Q, Zhijuan D, Jian J, Cong Z, Yingying Z, Chaoming W. Gene analysis and misdiagnosis of thyroid receptor β gene mutation in the pedigree with thyroid hormone resistance. J Wenzhou Med University. 2017;48(3):172-7.

24. Han R, Lei Y, Jiang X, Zhou X, Billon C, Guan W, et al. Characteristics of patients with late manifestation of resistance thyroid hormone syndrome: A single-center experience[J]. Endocrine. 2015;50(3):689-97.

25. Dong Q, Gong CX, Gu Y, Su C. A new mutation in the thyroid hormone receptor gene of a Chinese family with resistance to thyroid hormone. Chin Med J. 2011;124(12):1835-9.