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CASE REPORT

A novel thyroid hormone receptor alpha gene mutation, clinic characteristics, and follow-up findings in a patient with thyroid hormone resistance

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Abstract

Thyroid hormone receptor alpha (THRA) gene mutation is a thyroid hormone resistance syndrome characterized by near-normal thyroid function tests and tissue-specific hypothyroidism. In this case study, we report a novel de novo p.G291S heterozygous mutation in the THRA gene was detected at mutation analysis. A 4-year-old male patient was admitted due to short stature, motor-mental retardation, and constipation. At physical examination, coarse facial appearance, eyelid edema, pallor, and umbilical hernia were observed. Primary thyroid hormone resistance should be considered in patients with phenotypically hypothyroid features. Laboratory analysis found moderate elevation in free triiodothyronine (T3) levels, normochromic normocytic anemia, and elevated creatine kinase levels. In conclusion, THRA gene mutation should be considered in patients with clinical hypothyroid findings and increased/moderately elevated free T3, decreased/ normal free thyroxine, normal thyroid-stimulating hormone levels, and increased muscle enzymes.

Keywords Resistance to thyroid hormone · Thyroid hormone receptor alpha · Hypothyroid

Introduction

Thyroid hormones (TH) affect target tissues via specific nuclear receptors encoded by the TH receptor α (THRA) gene and TH receptor β (THRB) gene). THRA is a gene located on chromosome 17q11.2. TH receptor isoforms (TRα1, TRα2 and TRβ1, TRβ2, and TRβ3) are encoded by distinct genes (THRA and THRB). TR α1, and TR α2 are mainly located in the bones, cardiac and skeletal muscle, digestive tract and central nervous system [1]. Resistance to TH is characterized by non-responsiveness of peripheral tissues to the active form of TH (T3) [2].

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Two forms of inheritable RTH have been described—RTH β and RTH α. In > 85% of cases, RTH β is caused by a mutation in THRB [2]. The first case of THRA mutation was reported in 2012 in a 6-year-old girl with growth retardation [3].

We describe a novel THRA gene mutation in a patient with thyroid hormone resistance.

Case A 4-year-old male patient was admitted due to short stature, motor-mental retardation, and constipation. We were informed that motor-mental retardation had been assessed at the age of 1 year, but that no etiological cause had been identified. His medical history revealed that he was born at 38 weeks with a birth weight of 2900 g. Delayed motor-mental development stages and delayed tooth eruption were present. The parents were first-degree relatives. At physical examination, height, weight, and head circumference were 17.4 kg (SDS − 0.12), 96.4 cm (SDS − 2.47), and 54.5 cm (SDS 2.08), respectively. Umbilical hernia, coarse facial appearance, eyelid edema and pallor were observed. Laboratory values were hemoglobin 10.4 g/dl, red blood cell count (RBC) 4.6×10^6/μl, mean corpuscular volume (MCV) 88.5 fl, red cell distribution width (RDW) 14.7%, iron 123 μg/dl, total

iron-banding capacity 331 μg/dl, ferritin 28.9 mg/l (7–140), B12 220 ng/l (180–914), and folic acid 8.5 ng/ml (5–21), creatine kinase (CK) 396 IU/l (41–277), insulin-like growth factor (IGF-1) 44 ng/ml (−1.5–2 SD), and sex hormone-binding globulin (SHBG) 150.5 nmol/l (16–100), while electrolyte levels, liver, and kidney function tests and lipid parameters were all normal. Thyroid function test values were free triiodothyronine (T3) 5.04 pg/ml (2.3–4.2), free thyroxine (T4) 0.93 ng/dl (0.89–1.76), thyroid-stimulating hormone (TSH) 3.89 μIU/ml (0.35–5.5), and bone age 2 years. General thickening of the scalp was observed at craniography. Primary thyroid hormone resistance should be considered in patients with phenotypically hypothyroid features and moderate elevation in free T3 levels, normochromic normocytic anemia, and elevated CK levels at laboratory analysis. A novel de novo p.G291S heterozygous mutation in the THRA gene was detected at mutation analysis. Na-L thyroxin replacement therapy was started (1 μg/kg/day). After treatment, free T4 increased, no significant change was observed in free T3, and a moderate decrease in TSH and decreased CK levels were detected (Table 1).

At physical examination at the of age 6 years and 6 months, height, weight, and head circumference were 21.6 kg (SDS − 0.11), 109.8 cm (SDS − 1.85), and 55 cm (SDS 1.87), respectively. Growth velocity was 6.2 cm/year. Clinical amelioration in constipation was also observed.

Parental informed consent was obtained for publication of the case report.

Discussion

Although THRB mutations leading to thyroid hormone resistance are now well known, THRA mutations were not identified until recently. This may be due to the very rare occurrence of THRA mutations, and also failure to identify some cases.

The first patient with THRA mutation was reported in 2012 [3]. Fourteen different mutations in the THRA gene that result in RTHα have subsequently been described [3–12]. In our case, genomic DNA was extracted from peripheral blood leukocytes of the patient and his parents by using a MagNA Pure LC DNA Isolation Kit I (Roche Diagnostics, Mannheim, Germany) according to the manufacturer's protocol. All coding exons and exon-intron boundaries of the THRA gene were amplified by polymerase chain reaction (PCR). After purification of PCR products, mutational analysis was performed by direct sequencing of the coding exons and flanking introns of the THRA gene in an ABI PRISM 3500 genetic analyzer (Applied Biosystems, Foster City, California, USA). NM_003250 (GRCh37) reference sequence was used for THRA gene. While the father and mother had no variant, analysis of the patient revealed a c.871G>A (p.G291S) (Exon8) heterozygous change in the THRA gene (Fig. 1). This missense variant was not found in the Ensembl, dbSNP, and ClinVar variation databases nor in the Exome Sequencing Project (ESP), 1000 Genomes Project and Exome Aggregation Consortium (ExAC) population databases. It was interpreted as "disease causing" by the Mutation Taster Software (http://www.mutationtaster.org). We evaluated this variant as "likely pathogenic" according to the ACMG Standards and Guidelines recommendations [13]. Therefore, this report describes a case of a 4-year-old patient with a novel de novo p.G291S heterozygous mutation in the THRA gene (Table 2, Fig. 2).

Various clinical disorders such as developmental retardation, growth impairment, macroglossia, changes in bone ossification, and chronic constipation have to date been detected in RTHα patients, similarly to cases of untreated congenital hypothyroidism [3, 4, 6]. Additionally, the results of some cases support the hypothesis of a phenotype and genotype correlation. While intellectual disability is more common in cases with nonsense mutation, intellectual ability appears to be within normal ranges in cases with missense mutation [9]. In our case, the results of evaluations using the Wechsler Intelligence Scale for Children-Revised tests also indicated neurodevelopmental retardation.

Table 1 Biochemical measurements in the patient

	Baseline	1st month after treatment	1st year after treatment	2nd year after treatment	Reference values
Free T3 (pg/ml)	5.63	5.33	5.56	5.97	2.3–4.2
Free T4 (ng/dl)	0.96	1.10	1.20	1.30	0.89–1.76
TSH (mIU/l)	3.87	3.10	2.32	2.02	0.35–5.5
SHBG (nmol/l)	150.5	122.2	135.7	183	16–100
CK (IU/l)	396	260	267	250	41–171
IGF-1 (ng/ml)	44	38.7	50.4	39.3	73.2–154.9*

Abbreviations: *T3* triiodothyronine, *T4* thyroxine, *TSH* thyrotrophin-stimulating hormone, *SHBG* sex hormone-binding globulin, *CK* creatine kinase, *IGF-1* insulin-like growth factor 1

* 95% confidence interval values

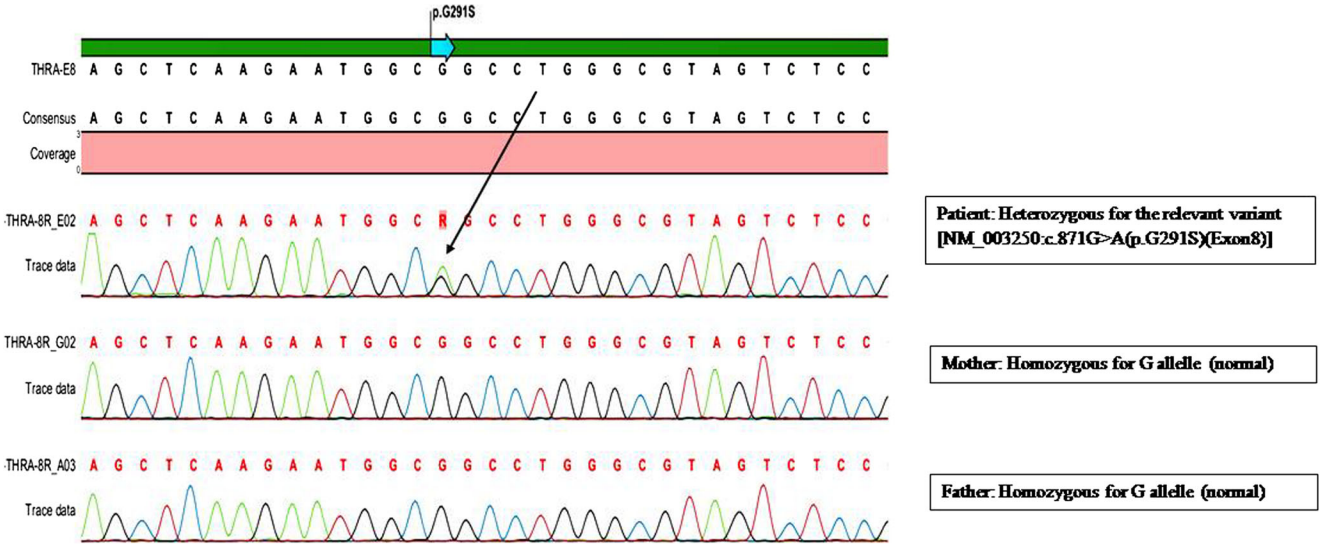

Fig. 1 Electropherogram of the patient and his parents for the relevant variant in the *THRA* gene

Our patient exhibited many clinical features that are typical of hypothyroidism (umbilical hernia, growth retardation, and constipation) but also, paradoxically, near-normal thyroxin levels, high triiodothyronine levels, and normal thyroid-stimulating hormone levels. THRA mutation is associated with skeletal abnormalities (growth retardation, delayed tooth eruption, and patent cranial sutures) as in the present case. Macrocephaly, which is thought to be related to cranial hyperostosis, has been demonstrated in our case and 11 other identified RTHα cases [14]. Impaired ossification is observed in THRA knockout mice and mouse models of RTH α. This has been attributed to a defect in cartilage growth and delayed maturation [15]. Growth retardation and delayed bone age in our case were associated with this condition. The characteristic Wormian bone appearance of the cranial sutures in hypothyroidism was also noted in our patient.

Increased parasympathetic activity and consequently reduced colonic motility have been described in previously reported RTHα patients [11, 14]. One of the principal symptoms in our case was constipation.

The relation between THRA mutations and the observed dyserythropoiesis is unclear. Studies have shown that inactivating mutations in TRα affect the balance between proliferation and differentiation in human erythroid progenitor cells. A below-normal RBC count, hypocellular bone marrow, and MCV at the upper limit of the normal range similar to macrocytic anemia in hypothyroidism may be detected with THRA mutations. Although mostly normocytic normochromic, anemia is a common characteristic in RTHα patients [16]. Normochromic normocytic anemia was detected in our case. Reduced RBC mass with mild anemia was documented in three patients with defective THRA, but the RBC count was normal in our case.

Elevated CK levels similar to those observed in hypothyroidism may be seen in patients with THRA mutation, suggesting that skeletal muscle was refractory to thyroid hormone action in our patient.

Improvement, albeit not total, in metabolic status, increased motor coordination, and accelerated growth as well as improvement in constipation have been reported with Na-L thyroxin therapy in THRA cases [6]. Na-L thyroxin therapy has had a beneficial effect on our patient, improving his constipation and general alertness and motor coordination. The mechanisms involved in the amelioration with age of deficits caused by THRA mutations are unclear.

Na-L thyroxin therapy has been recommended in the case of growth and neurodevelopmental retardation.

Table 2 pG291S mutation in THRA gene and its in silico analysis

THRA gen mutation	PolyPhen2 score	GERP score	FATHMM-MKL	ExAC*,# (overall allele frequency)	SIFT	Mutation tester
p.G291S c.871G>A	Probably damaging	4.96	Damaging	–	Damaging	Disease causing

*Exome Aggregation Consortium (http://exac.broadinstitude.org)

The allele frequency in the ExAC database does not contain representative controls for all ethnic groups

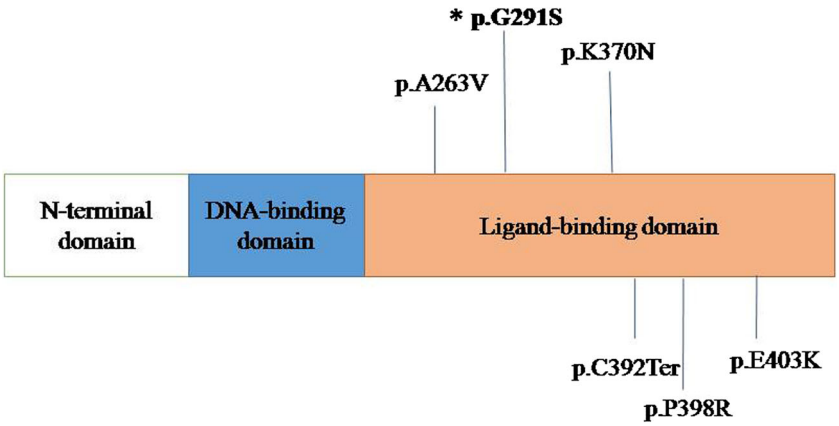

Fig. 2 Illustration of the *THRA* gene showing domains of the protein together with the known mutations. * indicates a novel variant

Response to treatment is better when this is started at an early stage [15]. Following Na-L thyroxin treatment, we observed moderate increases in serum-free T4 levels, decreases in TSH levels, no significant change in free T3 levels, and decreased CK levels in our patient. However, although in the early stage of treatment, a moderate decrease was observed in levels of SHBG, a peripheral marker of thyroid hormone effects, a moderate increase compared to baseline levels was determined in the long term, i.e., in the second year of treatment (Table 1). Moran et al. [6] reported slight increases in free T4 and free T3, suppressed TSH levels, and increased SHBG levels following thyroxin therapy. In our case, we detected a moderate change in thyroid functions posttreatment. We hypothesize that this may be related to the low Na-L thyroxin dose (1 μg/kg/day) administered. A previously described case of mutant THRA in a 6-year-old girl reported an increase in low basal IGF levels following Na-L thyroxin therapy. However, low-normal baseline IGF levels have been reported to remain unchanged following Na-L thyroxin therapy in other cases [8]. Low serum IGF-1 also remained unchanged with Na-L thyroxin therapy in our case. Our patient's elevated baseline CK level decreased with Na-L thyroxin therapy. Similar findings have been reported in other RTHα patients following thyroxin therapy and a decrease in CK levels. Mutant TRα injury in the skeletal muscular system may be treated with thyroid hormones [6, 8].

In conclusion, THRA mutations may be more common than currently thought. THRA gene mutation should therefore be considered in patients with clinical hypothyroid findings and moderate impairment in thyroid function tests. Long-term follow-up of clinical and laboratory findings of these patients will be useful in the diagnosis of new cases and treatment of these patients. Due to the increasing prevalence of RTHα, it is likely that knowledge about the genotype-phenotype of the disease will be expanded.

Authorship contributions Concept and design: Samim Ozen, Ozlem Korkmaz and Sukran Darcan; data collection and processing: Ozlem Korkmaz; analysis and interpretation: Ozlem Korkmaz, Taha Resid Ozdemir, Samim Ozen, Damla Goksen and Sukran Darcan; and literature research: Ozlem Korkmaz; writing: Ozlem Korkmaz and Samim Ozen. All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

Compliance with ethical standards

Conflict of interest None declared.

Informed consent Informed consent was obtained from the patients' parents for publication.

Honorarium None declared.

Employment or leadership None declared.

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