

Case report

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Persistent goiter with congenital hypothyroidism due to mutation in *DUOXA2* gene

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Thyroid hormones are crucial for development of the central nervous system. Congenital hypothyroidism (CH) is the most common preventable disease resulting in mental retardation. A neonatal screening test (NST) can detect a mild form of CH that can be treated at an early age. Generally after 3 years of age, when most of the brain has matured, clinicians consider reevaluation of thyroid function for CH patients that have been identified with a normal thyroid gland at a normal position. This report presents three CH patients that developed normally, with persistent goiter despite thyroid hormone supplements. The patients' initial thyroid-stimulating hormone (TSH) level after NST was 47, 157, and 57 mIU/L, respectively. Levothyroxine administration began at 1 or 2 months of age and was terminated after reevaluation at the age of 3, 15, and 5 years, respectively. However, 1 or 2 years later, they all resumed their medication due to increased TSH level coupled with newly developed or enlarged goiter. They all showed dual oxidase maturation factor 2 (*DUOXA2*) gene mutation: a homozygous mutation with *DUOXA2* (c.413dupA; p.Tyr138*) in case 1, a presumed compound heterozygotic mutation with *DUOXA2* (p.Tyr138*/p.Tyr246*) in case 2, and heterozygous mutations with *DUOXA2* (c.738C>G; p.Tyr246*) and *TPO* (c.2268dupT; p.Glu757*) in case 3. When goiter persists or is newly developed despite a maintained euthyroid status, for those with transient CH history, follow-up to assess the thyroid function is recommended for at least 1 or 2 years, and genetic testing would be helpful. This study presents the first clinical cases of *DUOXA2* mutation in Korea.

Keywords: Congenital hypothyroidism, Goiter, Genes

Introduction

Thyroid hormones affect the metabolism of all cells in the body and play a very important role in growth and neurodevelopment, particularly in children. Recently, the incidence of congenital hypothyroidism (CH) has increased to 1 in 1,000–2,000 live births worldwide, which has been confirmed by neonatal screening test (NST).¹⁾ CH is the most common disease that can be detected early, and appropriate treatment can prevent intellectual disability. Treatment is usually simple and inexpensive, mostly through prescription of thyroid hormone. Through early diagnosis and proper treatment, patients with CH can achieve normal height and intelligence.

Thyroid dysgenesis makes up about 75%–80% of etiology in CH cases, while dysmorphogenesis accounts for approximately 15%–20%.²⁻⁴⁾ Thyroid dysgenesis includes athyrosis, ectopic thyroid, and hypoplasia. Thyroid agenesis or ectopic thyroid usually requires permanent thyroid hormone supplement. Except for athyrosis, general treatment for CH is to maintain levothyroxine until 3 years of age, when most brain development is complete. Reevaluation of thyroid function at several weeks after drug cessation is helpful for deciding whether to continue with treatment. Due to NST, mild cases of CH can be detected and treated.

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If the thyroid appears to be in a normal position, mild CH patients can terminate treatment, which is meant for transient types of CH, usually considered as dys-hormonogenesis. Numerous studies have searched for a predictive variable between permanent and transient CH.^{5,6)} However, to date, no definite factor has been identified to differentiate permanent from transient forms of CH.

There are 7 steps in thyroid hormone biosynthesis: (1) transport of thyroid iodide, (2) thyroglobulin (Tg) synthesis, (3) oxidation and organification, (4) H₂O₂ generation, (5)

coupling of iodotyrosyl residues of Tg, (6) endocytosis of colloid and hormone (thyroxine [T₄], triiodothyronine [T₃], diiodotyrosine, monoiodotyrosine) release, and (7) recycling of iodide.⁴⁾ The following genes are related to thyroid hormone synthesis: *SLC5A5* (*NIS*), *SLC26A4* (*PDS*), *TG*, *TPO*, *DUOX2*, *DUOX2*, and *IYD*.^{4,7)} Goiter usually appears in CH when there is a defect in at least one of those genes. Determination of the genetic mutation causing CH assists in predicting whether the treatment will be permanent or transient. Park et al.⁸⁾ reported that *DUOX2* mutations are commonly detected in CH patients in Korea. They also identified oxidase maturation factor 2 (*DUOX2*) mutation, although they only counted the number and did not describe the phenotype.

We report 3 cases of *DUOX2* mutation in CH. This is the first clinical case report of *DUOX2* mutations in Korea.

Case reports

1. Case 1

A 4.5-year-old boy was referred to our clinic. He had received levothyroxine treatment for CH since 2 months of age. On his first visit to our clinic, he presented a huge goiter (7 cm×4 cm) (Fig. 1A) with elevated Tg (107.39 µg/L; reference range, 0–35 µg/L), although his thyroid function test (TFT) was normal (free T₄ [fT₄], 1.71 ng/dL; TSH, 3.24 mIU/L). His height was 109 cm (75th–90th percentile), body weight was 18.3 kg (50th–75th

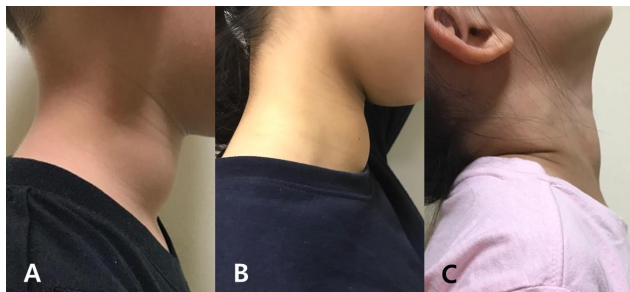


Fig. 1. (A) Case 1 developed a new goiter 1 year after stopping levothyroxine treatment. (B) Case 2 had a enlarged goiter 2 years after discontinuing levothyroxine. She still has the goiter despite a euthyroid state with taking levothyroxine. (C) Case 3 developed a new goiter 2 years after treatment cessation. All 3 patients resumed treatment and still have a goiter, while maintaining a euthyroid status.

Table 1. Clinical course and laboratory findings in the 3 cases

No	Age	FreeT ₄ (ng/dL)	TSH (mIU/L)	Tg (µg/L)	Tg-Ab (kIU/L)	Mic-Ab (kIU/L)	TBII (IU/L)	Goiter grade (size)	Treatment course
Case 1	NST*	1.05	47.14	NA	NA	NA	NA		
	1 mo	1.28	6.28	NA	NA	NA	NA	I (first detected)	
	2 mo	1.14	38.62	NA	NA	NA	NA	I ▲	Start T4 25 µg
	1 yr 6 mo	1.70	3.31	NA	NA	NA	NA	disappeared	During Tx.
	3 yr	1.78	5.26	NA	NA	NA	NA	I (reappeared)	Hold T4
	4 yr	1.15	24.34	NA	NA	NA	NA	II ▲	Restart T4
	4 yr 6 mo	1.71	3.24	107.39	0.52	0.13	0.01	II (7 cm × 4 cm) ▲	First visit to our clinic, T4 66 µg
4 yr 11 mo	1.37	2.99	NA	NA	NA	NA	II (5 cm × 3 cm) ▼	During Tx. T4 50 µg	
Case 2	NST*	NA	157.4	NA	NA	NA	NA		Start T4
	3 wk	5.48 [†]	>180	NA	NA	NA	NA		
	11 yr	1.38	3.59	120.95	0.03	0.08	0.00	II (7 cm × 5 cm)	First visit on our clinic, T4 60 µg
	13 yr 1 mo	1.31	2.71	61.21	NA	NA	NA	II (5 cm × 5 cm) ▼	During Tx. T4 75 µg
	15 yr 2 mo	1.15	6.02	163.57	0.15	0.17	0.50	II (5 cm × 5 cm)	Hold T4
	17 yr 2 mo	0.90	12.31	427.88	0.01	0.04	0.28	II (9 cm × 6 cm) ▲	Start Liothyronine 20 µg
	18 yr 2 mo	1.21	0.92	171.76	NA	NA	NA	II (7 cm × 5 cm) ▼	Restart T4 75 µg
18 yr 9 mo	1.49	1.31	NA	NA	NA	NA	II (5 cm × 4 cm) ▼	During Tx. T4 75 µg	
Case 3	NST*	NA	57.4	NA	NA	NA	NA		Start T4 33 µg
	20 day	1.56	29.59	NA	NA	NA	NA		
	4 mo	2.09	0.59	17.01	0.04	0.04	6.10	Goiter (-)	First visit on our clinic, T4 33 µg
	5 yr 3 mo	1.53	3.90	79.33	0.5	0.10	0.67	Goiter (-)	Hold T4 30 µg
	7 yr 3 mo	1.15	5.14	129.38	0.38	0.18	0.53	II (5 cm × 4 cm)	Restart T4 25 µg
	9 yr 6 mo	1.19	1.70	NA	NA	NA	NA	I (4 cm × 3 cm) ▼	During Tx. 25 µg

FreeT₄, free thyroxine; TSH, thyroid-stimulating hormone; Tg, thyroglobulin; Tg-Ab, antithyroglobulin antibody; Mic-Ab, antimicrosomal antibody; TBII, thyrotropin-binding inhibitory immunoglobulin; NST, neonatal screening test; NA, not available; T4, levothyroxine; Tx., treatment,

*NST was checked within 7 days after birth. [†]Total T₄.

percentile), and all developmental milestones were normal.

The patient was born at 38⁺⁵ weeks of gestation, with a birth weight of 3.48 kg. The initial neonatal screening TSH level was 47.14 mIU/L (reference range, <10 mIU/L), while the serum TSH level decreased to 6.28 mIU/L when he was 1 month old. One month later, not only had TSH level increased to 38.62 mIU/L, but goiter had developed, for which he was consequently started on levothyroxine. After commencement of treatment, his goiter was not palpable. When he reached 3 years of age, he was able to stop medication, as TFT results after 6 weeks of holding medication indicated normal ranges (fT4, 1.78 ng/dL; TSH, 5.26 mIU/L) with a palpable goiter. He resumed the medication at the age of 4 due to increased TSH level up to 24.34 mIU/L and because the goiter had become visible (Table 1).

We performed next-generation sequencing (NGS) for hypothyroidism that covers 23 related genes (*TSHR*, *PAX8*, *TSHB*, *NKX2-5*, *THRA*, *GNAS*, *FOXE1*, *NKX2-1*, *SLC5A5*, *TPO*, *TG*, *DUOXA2*, *DUOX2*, *SLC26A4*, *IYD*, *SLC16A2*, *THRβ*, *POU1F1*, *PROPI*, *LHX3*, *TSHB*, *HESX1*, *TRH*, *TRHR*) using Miseq (Illumina, San Diego, CA, USA) with 192X depth of coverage and greater than 99% accuracy. A homozygous mutation of *DUOXA2* with c.413dupA (p.Tyr138*) was identified (Fig. 2A). He was an only child, and his parents refused to undergo genetic analysis. After 11 months of

treatment, his goiter had slightly decreased (5 cm×3 cm) with normal TFT.

2. Case 2

An 11-year-old girl diagnosed with CH was referred to our hospital for a huge goiter (7 cm×5 cm) under levothyroxine medication. She was born at a gestational age of 39⁺⁰ weeks and body weight of 3.0 kg. The initial NST for TSH was 157.4 mIU/L and 225.6 mIU/L at 7 and 12 days old, respectively. She had started levothyroxine treatment at 3 weeks (total T4, 5.48 μg/dL [reference range, 4.5–12.5 μg/dL]; TSH >180 mIU/L). Her father, grandfather, and 3 uncles from her father's side had thyroid disease, though the exact diagnosis was unknown. The initial laboratory findings in our clinic were fT4 1.38 ng/dL; TSH 3.59 mIU/L; and Tg 120.95 μg/L. She had a height of 144.5 cm (50th–75th percentile), and a body weight of 42 kg (50th–75th percentile). She had normal intelligence and experienced menarche at the age of 12 with normal puberty progression. During persistent treatment with levothyroxine 75 μg, goiter size decreased to 5 cm×5 cm, and Tg level decreased (61.21 μg/L) compared to the initial level.

She was able to stop the treatment at 15 years of age, as her fT4 level was normal with mild elevation of TSH (6.02 mIU/

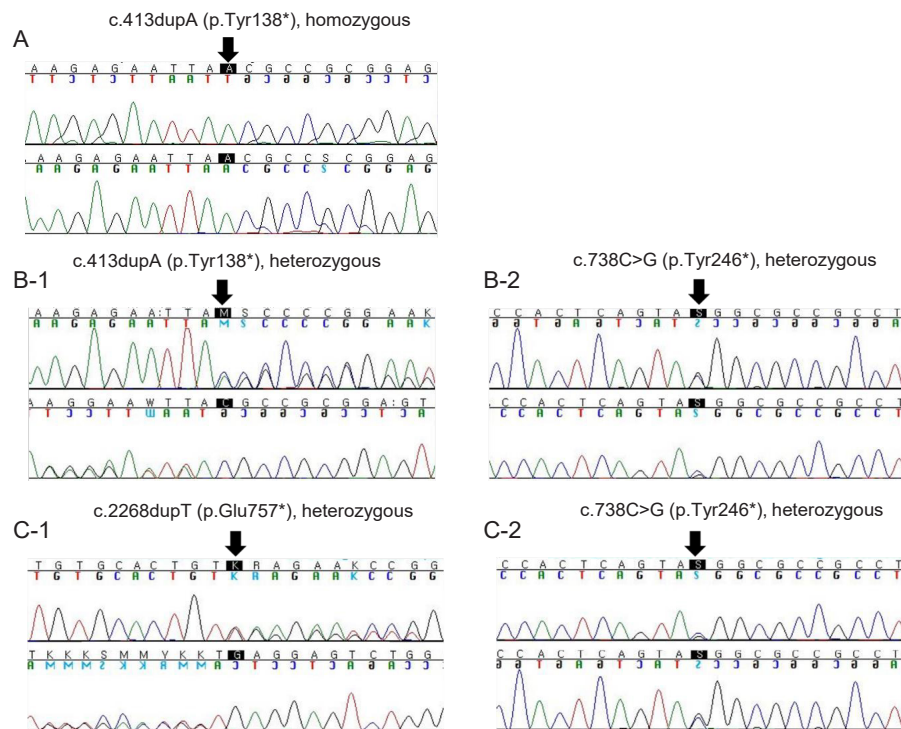


Fig. 2. Next-generation sequencing for hypothyroidism revealed genetic mutations. (A) A homozygous mutation with *DUOXA2* at c.413dupA (p.Tyr138*) was identified in case 1. (B) A presumed compound heterozygous mutation with *DUOXA2* at c.413dupA (p.Tyr138*) (B-1) and c.738C>G (p.Tyr246*) (B-2) was identified in case 2. The mutation was assumed to be compound heterozygous based on her clinical presentation, although there was no confirmation as her parents refused to undergo genetic analysis. (C) Heterozygous mutations of both *TPO* at c.2268dupT (p.Glu757*) (C-1) and *DUOXA2* at c.738C>G (p.Tyr246*) (C-2) were detected in case 3.

L) after 6 weeks of no medication. We assessed a normal TSH response of thyrotropin releasing hormone stimulation test. A ^{99m}Tc scan revealed increased uptake of 18.9% (reference range, 1.7%–4.0%). After 2 years, liothyronine 20- μg medication was restarted as she complained of tiredness with a repeated huge goiter (9 cm \times 6 cm) (fT4, 0.90 ng/dL; TSH, 12.31 mIU/L; Tg, 427.88 $\mu\text{g}/\text{L}$) (Table 1) (Fig. 1B). All thyroid antibodies were normal. The goiter decreased slightly (7 cm \times 5 cm) after treatment restarted.

An NGS test for hypothyroidism was performed, and two nonsense mutations of *DUOXA2*, c.413dupA (p.Tyr138*) and c.738C>G (p.Tyr246*), were identified (Fig. 2B). Genetic analysis was recommended to her parents to confirm whether her mutations were compound heterozygous. Although her parents refused to perform the test, there were apparent clinical interpretation matched her genetic mutation to be regarded as compound heterozygous state. After identifying the genetic cause of her CH and goiter, we changed her medication from liothyronine to levothyroxine.

Under treatment, goiter size decreased to 5 cm \times 4 cm, although it was still big. Currently, core needle biopsy is being planned for 2 newly detected hypochoic nodules (0.92 cm and 0.62 cm).

3. Case 3

A 4-month-old girl visited our clinic for CH treatment (fT4, 2.09 ng/dL; TSH, 0.59 mIU/L; Tg, 17.01 $\mu\text{g}/\text{L}$). She had started levothyroxine 20 days after birth (fT4, 1.56 ng/dL; TSH, 29.59 mIU/L). Her initial TSH level of NST was 57.4 mIU/L.

She was able to stop treatment at 5 years of age, as the TFT level was normal after 6 weeks without therapy (fT4, 1.53 ng/dL; TSH, 3.90 mIU/L; Tg, 79.33 $\mu\text{g}/\text{L}$). A ^{99m}Tc scan showed increased uptake of 6.9% (reference range, 1.7%–4.0%). At that point, goiter was neither visible nor palpable.

Two years later, however, a goiter (5 cm \times 4 cm) was detected by her mother. Her TFT result indicated subclinical hypothyroidism (fT4, 1.15 ng/dL; TSH, 5.14 mIU/L), and treatment with 25- μg levothyroxine was restarted (Table 1). An NGS test for hypothyroidism revealed heterozygous mutations for both *DUOXA2* [c.738C>G (p.Tyr246*)] and *TPO* [c.2268dupT (p.Glu757*)] (Fig. 2C). The patient had a younger brother who was treated for transient CH until 18 months of age. Her parents declined genetic testing for him and for themselves. The patient still has a goiter (4 cm \times 3 cm) and is under 25- μg levothyroxine medication with an euthyroid status (Fig. 1C).

Discussion

The 3 cases of CH presented in this study with *DUOXA2* mutations showed newly developed or enlarged goiter after terminating levothyroxine treatment. They all had to resume treatment due to increased TSH level within 1–2 years of

treatment cessation.

Both oxidation of iodide and iodination of Tg by thyroid peroxidase are important steps for synthesizing thyroid hormone. Hydrogen peroxidase (H_2O_2), produced at the apical membrane of thyroid follicular cells, is a critical substrate for both steps. The dual oxidases (DUOX1 and DUOX2) play important roles for catalyzing H_2O_2 formation.^{9,10} The *DUOXA2* gene, which is comprised of 6 exons and encodes a 320-amino acid transmembrane protein, is essential for DUOX2 maturation and activation. A mutation in *DUOXA2* was first discovered in 2008 in 11 CH patients with partial iodide organification defects without *TPO* or *DUOX2* mutation.¹¹ Mutation of *DUOXA2* affects partial or complete iodide organification that can lead to dysthyroidism.^{11–13} The phenotype associated with *DUOXA2* mutation is usually inherited in an autosomal recessive manner, although some reports suggest autosomal dominant inheritance.¹³ Regardless of inheritance, goiter is a characteristic clinical presentation. Because thyroid hormone production capacity is impaired, elevated TSH stimulates the thyroid follicular cells to compensate for defective function. This stimulation increases the Tg level as the thyroid enlarges to become a goiter. However, there is currently no clear explanation for why the goiter persists even with an euthyroid status in *DUOXA2* mutation.

Case 1 featured the previously reported nonsense homozygous *DUOXA2* (p.Tyr138*) mutation, a loss-of-function mutation. There was a report on Japanese siblings who had the same mutation but with a different phenotype.¹⁴ The younger sister started levothyroxine treatment after she was diagnosed with CH at 13 days old with a high serum Tg level (>1,000 $\mu\text{g}/\text{L}$; reference range, 3.8–56.3 $\mu\text{g}/\text{L}$) and a goiter confirmed through ultrasonography (thyroid size, +5.9 standard deviation [SD])¹⁵. She had to continue medication, because her TSH level elevated after stopping medication at 3 years of age. In comparison, her elder brother had a normal neonatal screening TSH result and a normal TFT at 10 years of age. Based on elevated Tg (106 $\mu\text{g}/\text{L}$; reference range, < 30 $\mu\text{g}/\text{L}$) and a slightly enlarged goiter observed on ultrasonography (thyroid size, +1.7 SD¹⁵), mild defect of thyroid hormone producing capacity was suspected. Similarly, case 1 had a normal TFT period of 1 year without medication, the same as in the elder brother. However, case 1 had to resume treatment due to increased TSH with enlarged goiter, which was similar to the younger sister's case. Therefore, based on these reports, there could be additional unknown factors regulating the expression of enzymatic activity.

Case 2 is regarded as a compound heterozygote *DUOXA2* (p.Tyr138*/p.Tyr246*) mutation, although the parents were not genetically tested. The same mutation was first described in 2013 from China.¹⁶ The mutation was detected in only 1 of 47 CH patients, and that patient was diagnosed with CH after NST, without a report of goiter. Recently, the same mutation was reported in a goitrous hypothyroidism fetus treated with intrauterine levothyroxine injection.¹⁷ The goiter size in case 2 was the largest of our 3 reported cases, with the highest Tg level. To date, no reports have presented a correlation between thyroid

nodule or cancer and *DUOXA2* mutation. We are currently waiting for results for biopsies of the hypoechoic nodules.

Case 3 was identified to have each of the known pathogenic heterozygote mutations in *DUOXA2* (p.Tyr246*) and *TPO* (p.Glu757*). She started levothyroxine 33- μ g treatment at 20 days old and was on 25 μ g at 10 years old, the smallest amount of the three cases. A mild form of CH coupled with goiter suggests mild defect in organification in this case. Since both *TPO* and *DUOXA2* genes are inherited in an autosomal recessive manner, the identified mutations did not entirely explain the clinical aspects. Therefore, we considered large deletion/duplication or deep intronic mutation not indicated by the NGS test. Nonsense mutation p.Tyr246* is the first known pathogenic *DUOXA2* mutation, found in a Chinese female with homozygotic state.¹¹⁾ In that study, only heterozygotic mutation probands did not have TFT abnormality. In 2015, another Chinese female was

reported to have homozygotic state with goiter and elevated Tg level.¹³⁾

Because there are 2 *DUOXs* and 2 *DUOXAs* in the thyroid gland, transient improvement of thyroid function may be explained by a "backup" of *DUOX1/DUOX1A1* due to lower RNA expression levels compared to *DUOX2/DUOX2A2*.^{18,19)} *DUOX2* mutations are frequently associated with CH in Korea and Japan, and the prognosis is usually transient.^{2,8,20)} In contrast, *DUOX2A2* mutations are uncommon and seem to be more pathogenic compared to *DUOX2* mutations. Since 2008, when *DUOX2A2* was first detected,¹¹⁾ there have been 10 reported patients, most from China, Japan, or Korea (Table 2). Goiter appears to be consistent with lengthy treatment. However, a definite genotype-phenotype correlation is limited for the *DUOX2A2* mutation. Therefore, additional case studies and long-term follow-up are required.

Table 2. Summary of heterogenous genotype-phenotype correlation in *DUOXA2* mutation

No.	Mutation	Sex	Nationality	TSH at NST (mIU/L)	Initial serum TSH (mIU/L)	Initial serum ft4 (ng/dL)	Thyroid USG	Age at reevaluation	Serum TSH (mIU/L)	Serum ft4 (ng/dL)	Prognosis	References
1	p.Tyr246* (homozygous)	F	Chinese	48	12	39 [*]	Goiter	7 yr	5.0	1.7	Restart Tx. 8 months later	Zamproni et al. ¹¹⁾
2	p.Cys189Arg (gene deletion ↑)	M	German	58	151	5.2 [*]	Goiter	2 yr	5.3	1.4	Euthyroid until 1 year after Tx. stopped	Hulur et al. ⁹⁾
3	p.Tyr138*/p.Tyr246* (compound heterozygous)	NA	Chinese	NA	NA	NA	NA	NA	NA	NA	NA [†]	Yi et al. ¹⁶⁾
4	p.Ile26Met (heterozygous)	F	Chinese	49	59.4	0.32	Normal	2 yr	WNL	WNL	Stopped Tx.	Liu et al. ¹³⁾
5	p.Tyr246* (homozygous)	F	Chinese	135	129	0.22	Goiter	2 yr	6.5	NA	Restart Tx. 1 month later	Liu et al. ¹³⁾
6	p.Tyr138* (homozygous)	M	Japanese	WNL	NA	NA	Goiter	9 yr	2.0	1.1	No Tx.	Sugisawa et al. ¹⁴⁾
7	p.Tyr138* (homozygous)	F	Japanese	78	138	0.4	Goiter	3 yr	11.0	1.2	Continue Tx.	Sugisawa et al. ¹⁴⁾
8	p.Tyr138*/p.Tyr246* (compound heterozygous)	M	Japanese	NA	253 [‡]	0.29 [‡]	Goiter (fetal onset)	NA	NA	NA	Continue Tx.	Tanase-Nakao, et al. ¹⁷⁾
9	p.Tyr138* (heterozygous)	F	Korean	NA [§]	NA	NA	NA	NA	NA	NA		Park et al. ⁸⁾
10	p.Arg50Cys/p.Tyr138* (compound heterozygous)	F	Korean	NA [§]	NA	NA	NA	NA	NA	NA		Park et al. ⁸⁾
11	p.Tyr138* (homozygous)	M	Korean	47	38	1.14	Goiter	3 yr	5.26	1.78	Restart Tx. 1 yr later	Present case 1
12	p.Tyr138*/p.Tyr246* (presumed compound heterozygous)	F	Korean	157	>180	5.48	Goiter	15 yr	6.02	1.15	Restart Tx. 2 yr later	Present case 2
13	p.Tyr246* (heterozygous) +mutation in <i>TPO</i> (p.Glu757*, heterogenous)	F	Korean	57	29	1.56	Goiter	5 yr	3.9	1.53	Restart Tx. 2 yr later	Present case 3

TSH, thyroid-stimulating hormone; NST, neonatal screening test; ft4, free thyroxine; USG, ultrasonography; Tx., treatment; NA, not available; WNL, within normal limit.

^{*}Total T4 (reference range, 4.5–12.5 μ g/dL). [†]This case was described as only "mild congenital hypothyroidism symptoms". [‡]Both initial TSH and free T4 were measured in percutaneous umbilical cord blood when the fetus was GA 34^{††} weeks. [§]They were described as prematurity only.

All three cases required resumption of levothyroxine treatment 1–2 years after treatment cessation. In conclusion, regular follow-up for TFT and physical examination of enlarged or newly developed goiter are recommended for at least 1 or 2 years after patients who terminate transient CH treatment. Additionally, genetic analysis is helpful to determine the cause of goiter.

Ethical statement

This study was approved by the Institutional Review Board of Soonchunhyang University Seoul Hospital (approval number: 2019-03-021). The parents of all cases offered informed written consent for genetic tests and using the results and photographs obtained from the patients.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

Acknowledgments

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