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Identification of Mutations in the Thyroxine-Binding Globulin (TBG) Gene in Patients with TBG Deficiency in Korea

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Background: Thyroxine-binding globulin (TBG) is a major transporter protein for thyroid hormones. The serpin family A member 7 (*SERPINA7*) gene codes for TBG, and mutations of the *SERPINA7* gene result in TBG deficiency. Although more than 40 mutations have been reported in several countries, only a few studies of TBG deficiency and *SERPINA7* gene mutation have been performed in Korea. The aim of this study is to review the clinical presentations and laboratory findings of patients with TBG deficiency and to investigate the types of *SERPINA7* gene mutation.

Methods: Five unrelated Korean adults with TBG deficiency attending endocrinology clinic underwent *SERPINA7* gene sequencing. Four patients harbored a *SERPINA7* gene mutation. Serum thyroid hormones, anti-microsomal antibodies, and TBG were measured. Genomic DNA was extracted from whole blood. All exons and intron-exon boundaries of the TBG gene were amplified and sequencing was performed.

Results: Two patients were heterozygous females, and the other two were hemizygous males. One heterozygous female had coexisting hypothyroidism. The other heterozygous female was erroneously prescribed levothyroxine at a local clinic. One hemizygous male harbored a novel mutation, p.Phe269Cysfs*18, which caused TBG partial deficiency. Three patients had the p.Leu372Phefs*23 mutation, which is known as TBG-complete deficiency Japan (TBG-CDJ) and was also presented in previous mutation analyses in Korea.

Conclusion: This study presents four patients diagnosed with TBG deficiency and provides the results of *SERPINA7* gene sequencing. One novel mutation, p.Phe269Cysfs*18, causing TBD-partial deficiency and three cases of TBG-CDJ were demonstrated. It is necessary to identify TBG deficiency to prevent improper treatment. Also, sequencing of the *SERPINA7* gene would provide valuable information about the TBG variants in Korea.

Keywords: Thyroxine-binding globulin; SERPINA7 protein, human; Thyroxine-binding globulin deficiency; Inherited thyroxine-binding globulin deficiency

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INTRODUCTION

Thyroxine-binding globulin (TBG) is a major thyroid hormone binding protein that binds to approximately 70% of triiodothyronine (T3) and 75% of thyroxine (T4) in serum [1-4]. TBG, a 54-kDa glycoprotein with a single chain of 395 amino acids, is synthesized in the liver. It is encoded by four exons in single gene called serpin family A member 7 (*SERPINA7*) which is located on the long arm of the X-chromosome (Xq22.2) [5]. TBG mutations have three phenotypes of TBG-complete deficiency (TBG-CD), TBG partial deficiency (TBG-PD), and TBG excess (TBG-E). TBG-CD is a rare condition harboring undetectable TBG concentration with a frequency of 1 in 15,000 newborns. TBG-PD is the most common phenotype among the TBG deficiencies with a frequency of 1 in 4,000 newborns [6-8]. The affected patients present clinically euthyroid status but show abnormal results in thyroid function tests (TFT) which can lead to misdiagnoses and improper treatment. Because TBG mutations are inherited in X-linked fashion, TBG deficiency is fully expressed in hemizygous males and homozygous females and less expressed in heterozygous females whose TBG concentration can overlap with the normal range [9].

To date, 49 mutations in the *SERPINA7* gene have been reported to cause TBG deficiency [10-14]. In Korea, reports of TBG deficiency mainly discuss neonates and pediatric patients, and only a few mutation analyses of the *SERPINA7* gene have been conducted. Park et al. [15] performed a mutation analysis in two neonates and revealed a single nucleotide deletion of codon 352 in exon 4, which is a prevalent variant in the Japanese population, called TBG-complete deficiency Japan (TBG-CDJ) [15,16]. A mutation analysis of an 11-year-old boy with TBG-CD by Baek et al. [17] also found the TBG-CDJ mutation. Pappa et al. [14] provided a summary of all TBG mutations reported to date including a Korean variant named TBG-PDKa that caused TBG-PD. However, because TBG-PDKa was not published in the literature, clinical information such as patient age, sex, habitation, comorbidities, and medication are unknown. In this study, we review the clinical presentations and laboratory findings of adult patients with TBG deficiency in Korea, and investigate the types of *SERPINA7* gene mutation through direct sequencing.

METHODS

Patients

Five unrelated Korean patients with TBG deficiency attending endocrinology clinic at Samsung Medical Center underwent *SERPINA7* gene sequencing with informed consents between June 2021 and March 2022. Four of the five patients, two males and two females, harbored *SERPINA7* gene mutations, and one of them presented a novel mutation. This study was approved by the Institutional Review Board of Samsung Medical Center (SMC-IRB 2021-06-134).

Measurement

Total T4, total T3, free T4, free T3, thyroid stimulating hormone (TSH), anti-microsomal antibody (AMA) and TBG were measured using the immunoradiometric assay (IRMA), radioimmunoassay (RIA), and electrochemiluminescence immunoassay (ECLIA) techniques.

Polymerase chain reaction amplification and direct sequencing

Blood specimens were collected from the study patients to for *SERPINA7* sequencing. Using a Wizard genomic DNA purification kit, genomic was extracted from whole blood in accordance with the manufacturer's instructions (Promega, Madison, WI, USA). All intron-exon boundaries and exons of the *SERPINA7* gene were amplified, and direct sequencing was conducted using an ABI Prism 3100 GeneticAnalyzer (Applied Biosystems, Waltham, MA, USA) with a BigDye terminator cycle sequencing-ready reaction kit (Applied Biosystems). The primer sets used for direct sequencing are shown in Supplemental Table S1. The nucleotides and corresponding protein sequences were represented in accordance with the reference sequences of NM_000354.6 and NP_000345.2, respectively. The pathogenicity of the variants was analyzed with the Single Nucleotide Polymorphism Database (dbSNP) 147, Clinvar, and Human Gene Mutation Database (HGMD). The population frequency was acquired through gnomAD v.2.1.1 and the Korean Reference Genome Database (KRGDB, accessed on October 15, 2021). The variants were classified into five groups following the American College of Medical Genetics and Genomics/Association for Molecular Pathology (ACMG/AMP) guidelines.

RESULTS

Case series

Case 1

This female patient was 47-year-old when she first visited endocrinology clinic of Samsung Medical Center after long-term fluctuation in thyroid function. The patient had been diagnosed

with hypothyroidism at a local clinic in 2018. Otherwise she had no remarkable medical history while her mother and sister had hypothyroidism. In the 2nd year of taking levothyroxine, her T3 level remained low, and her levothyroxine dosage was increased. Fatigue, palpitation, hand tremor and excessive weight loss of 10 kg followed the dosage increase. Failure to adjust appropriate dosage of levothyroxine led the patients to our endocrinology clinic on November 3, 2020. The serum free T4 and TSH levels reported at the local clinic shortly before her visit to our clinic were 2.09 ng/dL (normal range, 0.79 to 1.86) and 0.03 μIU/mL (normal range, 0.3 to 6.00), respectively, while on 88 μg of levothyroxine. No abnormal feature was observed in physical examination, thyroid ultrasonography, or thyroid scintigraphy. The AMA, thyroglobulin antibody, and anti-TSH receptor antibody were all within normal range. Measurement of TBG showed a decreased level of 5.35 μg/mL (normal range, 10.90 to 43.20). Levothyroxine was gradually tapered off. About 3 months after discontinuation of levothyroxine, she had no signs or symptoms of hypothyroidism, and her free T4, TSH, and total T3 were 1.16 ng/dL (normal range, 0.79 to 1.86), 6.58 μIU/mL (normal range, 0.3 to 6.00), and 42.2 ng/dL (normal range, 76 to 190), respectively. Upon diagnosis of TBG deficiency rather than hypothyroidism, sequencing of the *SERPINA7* gene was conducted. As a result, a 1-bp deletion (c.1114del) in exon 5 was detected.

Case 2

A 44-year-old male presented with decreased levels of total T3 of 64 ng/dL (normal range, 80 to 200) and total T4 of 3.7 μg/dL (normal range, 5.1 to 14.1) during a routine health examination in 2001 at Samsung Medical Center. His TSH was 1.14 μIU/mL (normal range, 0.3 to 6.00). The patients had no medical or family history. He did not present symptoms of hypothyroidism or thyrotoxicosis, and no abnormal findings were observed in physical examination. Thyroid ultrasonography revealed nothing significant. His AMA, thyroglobulin antibody, and anti-TSH receptor antibody levels were all within the normal range. Thereafter, decreased levels of total T3 and T4 were consistently observed in TFTs conducted every 1 to 2 years. Elevated free T4 without any symptoms or signs of thyrotoxicosis was observed episodically, and that led him to visit our endocrinology clinic in 2017, when he was 61-year-old. His TBG level was 1.42 μg/mL (normal range, 10.90 to 43.20), and under the diagnosis of TBG deficiency, TFTs have been performed every year without any treatment. The result of sequencing of *SERPINA7* gene was a 1-bp deletion (c.1114del) in exon 5.

Case 3

A 41-year-old female visited a local clinic in 2011 because of anterior neck discomfort and eyelid swelling. Testing of her thyroid function revealed hypothyroidism with TSH above 100 μIU/mL (normal range, 0.3 to 6.00) and decreased free T4 of 0.18 ng/dL (normal range, 0.79 to 1.86). She visited our endocrinology clinic after initiation of levothyroxine 100 μg. We adjusted her dosage to 75 μg. TSH was suppressed to 0.059 μIU/mL (normal range, 0.3 to 6.00), whereas total T3 level stayed low, with a value of 74.01 ng/dL (normal range, 76 to 190). Her AMA and thyroglobulin antibody were both positive with values of 133.1 U/mL (normal range, 0 to 60) and 835.3 U/mL (normal range, 0 to 60), respectively. Thyroid ultrasonography showed diffuse parenchymal changes suggestive of thyroiditis. She did not have any other medical history except hypothyroidism. Her son was also diagnosed with hypothyroidism. While being treated with 50 μg of levothyroxine, her total T3 level was constantly low, but her free T4 and TSH levels were in the normal ranges. Testing for TBG showed a decreased concentration of 5.47 μg/mL (normal range, 10.90 to 43.20), which produced a diagnosis of hypothyroidism combined with TBG deficiency. The *SERPINA7* gene sequencing revealed a 1-bp deletion (c.1114del) in exon 5.

Case 4

A 61-year-old male showed low total T3 in the TFTs of his routine health check-ups beginning in 2013, though his free T4 and TSH levels were in the normal ranges. Consequently, he was referred to our endocrinology clinic in 2021. He did not have any medical or family history, and he was not on any medication. Physical examination and review of system revealed no abnormal findings. Thyroid ultrasonography also presented normal thyroid volume and parenchyma. At his first visit to our endocrinology clinic, his TSH, total T3, and free T4 were 2.62 μIU/mL (normal range, 0.3 to 6.00), 48.8 ng/dL (normal range, 76 to 190), and 1.16 ng/dL (normal range, 0.79 to 1.86), respectively. His AMA, thyroglobulin antibody, and anti-TSH receptor antibody levels were all within normal ranges. His TBG level was low as 5.16 μg/mL (normal range, 10.90 to 43.20), which led to a diagnosis of TBG deficiency. Sequencing of *SERPINA7* gene showed a 2-bp deletion (c.806_807del) in exon 3.

Result of *SERPINA7* gene sequencing

The results of sequencing of the *SERPINA7* gene of the four study patients are shown in Fig. 1. In heterozygous female patient 1 and 3, and in hemizygous male patient 2, a 1-bp deletion

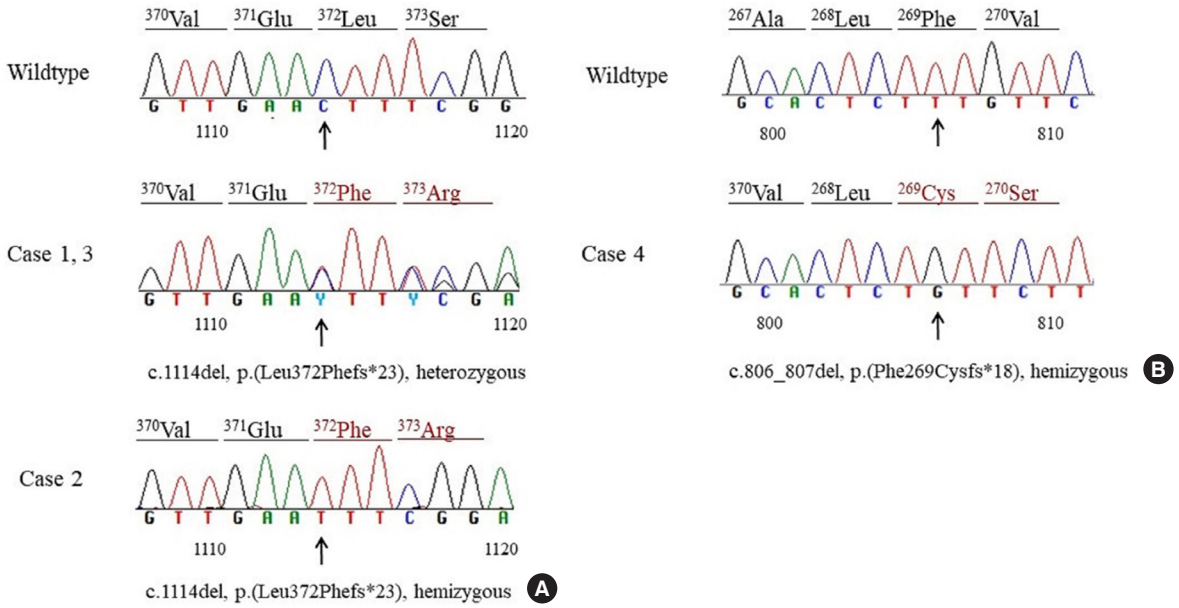

Fig. 1. Sanger sequencing chromatogram of the serpin family A member 7 (*SERPINA7*) variants detected in this study. (A) c.1114del variant was detected in heterozygous patient 1 and 3 and in hemizygous patient 2. (B) A novel hemizygous 2-bp deletion variant, c.806_807del, was detected in patient 4. Electropherograms of a wildtype and the proband are demonstrated. The positions of the deletion are indicated by arrows. The predicted amino acid translation is shown above the sequence. Altered codons in the proband are shown in red.

(c.1114del) in exon 5 was detected. The deletion was predicted to cause a frameshift and generate a premature stop codon 23 amino acids downstream of the variant position [p.(Leu372Phefs*23)]. Codon 372 occurs in the middle of the last coding exon (exon 5), meaning that it would escape nonsense-mediated mRNA decay. Because the variant is predicted to remove less than 10% of the protein product (22/415 amino acids), pathogenic and very strong (PVS1) was applied at a moderate evidence level. The allele frequency in the control database (0.0002 in gnomAD East Asian) was below the maximum credible population allele frequency (0.002) calculated using the alleleFrequencyApp tool [18] with 1:4,000 for prevalence and setting allelic heterogeneity to 0.1, genetic heterogeneity to 1, and penetrance to 50% [14,19]. This variant has previously been reported in other patients affected with complete TBG deficiency in the Japanese population [16,20]. Therefore, this frameshift variant was classified as a likely pathogenic variant (PVS1_moderate+pathogenic and moderate [PM2]+pathogenic and strong [PS4]) [21].

In patient 4, sequencing of *SERPINA7* gene revealed a hemizygous 2-bp deletion (c.806_807del) in exon 3 (Fig. 1). The deletion was predicted to cause a frameshift and generate a premature stop codon 18 amino acids downstream of the variant position, resulting in nonsense-mediated decay [p.(Phe269Cysfs*18)]. This variant was not found in control databases, such as the gnomAD (East Asian population) and KRGDB, nor has it been previously reported. Therefore, this novel frameshift variant was classified as a likely pathogenic variant (PVS1+PM2) [21].

Summarized baseline characteristics, lab findings, and courses

The results of the baseline characteristics, TFTs, TBG, thyroid autoantibodies, and direct sequencing of the *SERPINA7* gene of the four study patients are provided in Table 1. At their first visit to our endocrinology clinic, the patients ranged from 47 to 64 years of age. In terms of mutations, patient 1 and 3 were heterozygous females, and patient 2 and 4 were hemizygous males. Patient 1, 2, and 3 harbored a known mutation, p.Leu372Phefs*23 (TBG-CDJ), which is a prevalent mutation type in Japan. Patient 4 presented a novel mutation, p.Phe269Cysfs*18, causing TBG-PD. Only patient 3 had coexisting hypothyroidism. Patient 1 and 3 had a family history of hypothyroidism, but additional sequencing of the family members was not performed.

As demonstrated in Tables 2, 3, patient 1 and patient 3 were taking levothyroxine when visited to our endocrinology clinic. Patient 1 eventually tapered off levothyroxine, whereas patient 3 kept taking levothyroxine due to coexisting hypothyroidism.

Table 1. The Results of Baseline Characteristics, Thyroid Function Tests, TBG, Thyroid Autoantibodies, and Results of Direct Sequencing of *SERPINA7* Gene

Subjects	Sex	Age, yr	Genotype	Mutation	Coexisting hypothyroidism	Family history of hypothyroidism	Total T3, ng/dL (76–190)	FT4, ng/dL (0.79–1.86)	TSH, μIU/mL (0.3–6.00)	FT3, pg/mL (1.63–3.78)	Total T4, μg/dL (5.1–14.1)	TBG, μg/mL (10.90–43.20)	AMA, U/mL (0–60)	Tg Ab, U/mL (0–60)
Patient 1	F	47	Heterozygous	c.1114del, p.(Leu372Phefs*23)	None	Mother, sister	54.8±11.8	1.3±0.3	3.4±2.9	3.5±0.1	1.3	5.1±0.3	Negative	Negative
Patient 2	M	61	Hemizygous	c.1114del, p.(Leu372Phefs*23)	None	None	55.8±10.6	1.8±0.3	2.0±0.9	2.83	2.9±0.7	1.42	Negative	Negative
Patient 3	F	41	Heterozygous	c.1114del, p.(Leu372Phefs*23)	Hypothyroidism	Son	56±10.5	1.4±0.2	2.1±2.3	2.97	3.5	5.47	Positive	Positive
Patient 4	M	61	Hemizygous	c.806_807del, p.(Phe269Cysfs*18)	None	None	58.9±8.9	1.3±0.2	4.1±1.3	4.97	1.7	5.16	Negative	Negative

Values are expressed as mean±standard deviation.
TBG, thyroxine-binding globulin; *SERPINA7*, serpin family A member 7; T3, triiodothyronine; FT4, free thyroxine; TSH, thyroid stimulating hormone; FT3, free triiodothyronine; T4, thyroxine; AMA, anti-microsomal antibody; Tg Ab, thyroglobulin antibody.

Table 2. The Detailed Thyroid Hormones and Dosage of Levothyroxine of Patient 1

Visit	Days from the first visit	Total T3, ng/dL (76–190)	FT4, ng/dL (0.79–1.86)	TSH, μIU/mL (0.3–6.00)	FT3, pg/mL (1.63–3.78)	Total T4, μg/dL (5.1–14.1)	TBG, μg/mL (10.90–43.20)	Levothyroxine dose, μg
1	0	58.5	1.78	0.3				75
2	51	61	1.46	0.65	3.59		5.35	75
3	126	43.1	1.3	4.09				50
4	188	69.3	1.03	5.6				25
5	262	42.2	1.16	6.58	3.49	1.3	4.86	Tapered off
Mean±SD		54.8±11.8	1.3±0.3	3.4±2.9	3.5±0.1		5.1±0.3	

T3, triiodothyronine; FT4, free thyroxine; TSH, thyroid stimulating hormone; FT3, free triiodothyronine; T4, thyroxine; TBG, thyroxine-binding globulin; SD, standard deviation.

DISCUSSION

In this study, direct sequencing of the *SERPINA7* gene was conducted in five unrelated adults with TBG deficiency from a tertiary center in Korea. Four of those patients harbored *SERPINA7* gene mutation, one novel mutation of p.Phe269Cysfs*18 and three known mutations of p.Leu372Phefs*23. The affected females, patient 1 and 3, were heterozygous for the mutation. Patient 4, a hemizygous male had a novel mutation and presented a TBG level of 5.16 μg/mL, which is similar to the levels of heterozygous females, suggesting that the novel mutation p.Leu372Phefs*23 caused TBG-PD.

This study is, to our knowledge, the first published *SERPINA7* gene mutation analysis reporting a novel mutation other than TBG-CDJ in Korea and the first to be performed exclusively on unrelated adults in Korea. As summarized in Table 4, nine studies reporting TBG deficiency were previously conducted, and four of them performed *SERPINA7* gene sequencing, of which the results were all TBG-CDJ [15,17,22-28]. A summarized report by Pappa et al. [14] about all genetically identified TBG mutations contained a variant of TBG-PD caused by a G to A transition of codon 74 in exon 1 of the *SERPINA7* gene which replaced glutamic acid to lysine. That mutation was designated as a Korean variant (PDKa) in that study; however, it was impossible for us to verify any reference among the published papers.

Considering that TBG-CD is defined as undetectable TBG (below 5 μg/mL or 0.003% the average normal) [29] in a hemizygous patient where only mutant allele is expressed, the new p.Phe269Cysfs*18 mutation is regarded to cause TBG-PD. However, it is unusual that this mutation resulted in TBG-PD rather than TBG-CD. Most cases of TBG-CDs are caused by nucleotide deletion like the novel mutation in this study, and point mutation is the only reported mechanism to cause TBG-

Table 3. The Detailed Thyroid Hormones and Dosage of Levothyroxine of Patient 3

Visit	Days from the first visit	Total T3, ng/dL (76–190)	FT4, ng/dL (0.79–1.86)	TSH, μIU/mL (0.3–6.00)	FT3, pg/mL (1.63–3.78)	Total T4, μg/dL (5.1–14.1)	TBG, μg/mL (10.90–43.20)	Levothyroxine dose, μg
1	0	37.2	1.29	1.05				100
2	33	61.09	1.2	7.15				50
3	89	66.21	1.57	0.59				75
4	251	56.7	1.28	3.67				75
5	656	74.01	1.79	0.059				75
6	866	47.8	1.51	1.088				50
7	1,048	57.48	1.58	0.131				50
8	1,234	56.61	1.46	1.589				50
9	1,594	44.54	1.39	1.345				50
10	1,980	41.2	1.37	0.612				50
11	2,246	42.5	1.2	2.26			5.47	50
12	2,435	66.27	1.44	0.533				50
13	2,620	64.29	1.29	7.802				50
14	3,012	62.5	1.37	2.24				50
15	3,402	56	1.39	1.62				50
16	3,764	61.8	1.32	1.67	2.97	3.5		50
Mean±SD		56±10.5	1.4±0.2	2.1±2.3				

T3, triiodothyronine; FT4, free thyroxine; TSH, thyroid stimulating hormone; FT3, free triiodothyronine; T4, thyroxine; TBG, thyroxine-binding globulin; SD, standard deviation.

Table 4. Summary of Previous Reports of TBG Deficiency and Mutation Analysis in Korea

Study	Year	Subject	No. of subjects	Age	Reason for TBG testing	Coexisting thyroid function abnormality	Phenotype	Sequencing	Sequencing in family member (variant)
Jo et al. [25]	1995	Neonate	2	4.5 wk	Low T4 on screening	No	TBG-CD	Not done	
Lee et al. [28]	1996	Neonate	2	1 mo	Low T4 on screening	No	TBG-CD	Not done	
Park et al. [15]	2005	Neonate	2	3.5 wk	Low T4 on screening	No	TBG-CD	TBG-CDJ	
Lee et al. [24]	2015	Neonate	32	35.8 day	Low T4 on screening	Hypothyroidism (18/32)	TBG-CD	Not done	
Baek et al. [17]	1996	Child	1	11 yr	Not specified	No	TBG-CD	TBG-CDJ	Mother (TBG-CDJ)
Lee et al. [27]	2002	Child	1	22 mo	Low T4 on screening	Hypothyroidism	TBG-CD	Not done	
Ihm et al. [23]	1995	Adult	2	36, 51 yr	Low T3 and T4	No	TBG-CD	TBG-CDJ	Two siblings (TBG-CDJ)
Kim et al. [22]	2009	Adult	1	28 yr	Normal T3, low TSH, high free T4	Graves' disease	TBG-CD	TBG-CDJ	
Hur et al. [26]	2011	Adult	1	68 yr	Low total T3/T4 and high free T4	No	TBG-CD	Not done	

TBG, thyroxine-binding globulin; T4, thyroxine; TBG-CD, thyroxine-binding globulin complete deficiency; TBG-CDJ, thyroxine-binding globulin complete deficiency Japan; T3, triiodothyronine; TSH, thyroid stimulating hormone.

PD so far [14]. Notably, the locus of this novel mutation is between those of the two mutations causing TBG-CD, TBG-CD Poland and TBG-CDJ [16,30]. Meanwhile, some cases of TBG-CDs are also caused by point mutations causing protein trunca-

tion [31-33]. Other factors such as protein folding or secretion can also affect the phenotype, so a protein structural analysis will help to verify the mechanism of the discordance in the novel mutation.

The natural course until the diagnosis of TBG deficiency in our study subjects was well described here. Patient 1 was erroneously diagnosed with hypothyroidism and was on levothyroxine, and she eventually was tapered off levothyroxine after being diagnosed with TBG deficiency. Patient 3 was initially diagnosed with hypothyroidism, but because TSH was suppressed as the levothyroxine dosage was increased but T3 remained consistently low, TBG deficiency was suspected. Generally, TBG deficiency is suspect when total thyroid hormones are low while free T4 and TSH are normal [14]. TBG deficiency exhibits clinically euthyroid status and does not require treatment. However, physicians unaware of this condition could misdiagnose TBG deficiency as hypothyroidism [12,34,35], despite this rarely occurs in endocrinologist's practice. Recognizing TBG deficiency is important because misdiagnosis for hypothyroidism might lead to iatrogenic thyrotoxicosis. When only total thyroid hormones level is low while TSH and free T4 are normal, history taking, checking symptoms of hypothyroidism, physical examination, and most importantly testing serum TBG level, along with thyroid autoantibodies or ultrasonography if necessary would help to avoid misdiagnosis.

This study has some limitations. First, it was conducted in a single medical center with a small number of study subjects. Therefore, it is insufficient to identify the pool of TBG variants in Korea. Second, no investigation of the mutational status of family members of the affected patients was conducted. Additional *SERPINA7* gene sequencing in immediate family members of the patient harboring the novel mutation is necessary, to help identify whether the mutation is *de novo* or inherited. However, a mutation analysis in unrelated subjects might be more representative than in family members, given that TBG variants other than TBG-CDJ had not been identified in Korea before this study.

In conclusion, this study presented four patients diagnosed with TBG deficiency and provided the results of *SERPINA7* gene sequencing. As a result, one novel mutation, p.Phe269Cysfs*18, causing TBD-PD and three cases of TBG-CDJ were found. Along with previous mutation analyses in Korea, this result suggests that TBG-CDJ could be a dominant variant in the Korean population. The novel mutation p.Phe269Cysfs*18 might also partially contribute to TBG variants in Korea, but further analyses of family members and other unrelated TBG deficiency patients is required. Early recognition of TBG deficiency in patients with discordant TFTs is necessary to prevent improper treatment. Although *SERPINA7* gene sequencing is not necessary to diagnose TBG deficiency, it could provide supplementary information about the TBG variants in Korea.

CONFLICTS OF INTEREST

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

AUTHOR CONTRIBUTIONS

Conception or design: J.H., H.J.R., H.P., T.H.K., J.H.C., S.W.K. Acquisition, analysis, or interpretation of data: J.H., S.M.K., H.D.P. Drafting the work or revising: J.H., S.M.K. Final approval of the manuscript: J.H., S.M.K., H.J.R., H.P., T.H.K., J.H.C., H.D.P., S.W.K.

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