

Partial Thyroid Hormone-Binding Globulin Deficiency: A Case Report and Literature Review

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Background: Thyroxine binding globulin (TBG) deficiency is a rare thyroid disease, mostly caused by genetic mutations and acquired by X-linked recessive inheritance. The clinical features of children with TBG deficiency and their family members were summarised and the *Serpina7* gene mutation was analysed, providing a reference for the differentiation of TBG deficiency.

Methods: Thyroid function was detected in TBG deficient patients, and genetic analysis was performed using polymerase chain reaction (PCR) and direct DNA sequencing to detect the characteristics of TBG mutants. Using “thyroxine binding globulin, gene and mutation” as keywords, PubMed (biomedical literature database), Web of Science and other databases were searched for relevant studies to collect and summarise relevant information.

Results: The TBG (14.7 µg/mL), 70% triiodothyronine (T3) (<0.3 nmol/L), total T3 (Tr3) (<0.05 ng/mL) and thyroxine (T4) (14.72 nmol/L) values were lower than normal, while the thyrotropin (TSH) (2.33 uIU/mL), free T3 (FT3) (1.62 pmol/L), and free T4 (FT4) (11.39 pmol/L) values were normal. These values indicate a TBG partially deficient phenotype. Using PCR amplification and direct sequencing of the target gene, a missense mutation in exon 4 of the *Serpina7* gene was found in the patient and the father, and the nucleic acid variant was C.909 (exon 4) g > T; the patient was heterozygous and the father was hemizygous. The literature search retrieved a total of 45 studies, most of which were related to mutations in the *Serpina7* gene. The mutation locations included exons, introns, enhancers and promoters, with exons the predominant location. A total of 49 variants of the *Serpina7* gene were identified.

Conclusion: *Serpina7* C.909G (P.L303F) is a mutation acquired from the father by X-linked recessive inheritance. The main clinical features of TBG deficiency patients are low serum T4, T3 and TBG levels, normal TSH, FT3 and FT4 levels, and no clinical manifestations.

Keywords: thyroxine-binding globulin, deficiency, genes, mutation

Introduction

Thyroxine-binding globulin (TBG) is the main binding protein of the thyroid hormone in the human body. It combines around 75% of thyroxine (T4) and 70% of triiodothyronine (T3).¹ Thyroxine-binding globulin deficiency is a rare thyroid disease, mostly caused by a gene mutation, and is generally acquired through X-linked recessive inheritance.² The gene encoding TBG is named the *Serpina7* gene, while it is also known as the TBG gene. It is located on Xq22.2, spans 5.5 kb and contains five exons. This gene encodes a 54 kDa protein, a mature protein containing 395 amino acids, and is glycosylated by four glycosyl chains after translation.³ The *Serpina7* gene mutation leads to the substitution of amino acid or the truncation of mature proteins, resulting in TBG deficiency or a decreased affinity with T4, or both.⁴ Genetic TBG defects, including changes in protein synthesis, secretion and stability, result in TBG variants.² Reports from different countries have described how these mutations in the coding and non-coding regions of the *Serpina7* gene lead to complete deficiency (TBG-CD) and partial deficiency (TBG-PD).⁵

Since the first report of the human *Serpina7* gene in 1986,⁶ a series of mutations and polymorphisms have been identified. According to different serum TBG concentrations in patients, TBG deficiency has three phenotypes: TBG-CD, TBG-PD and excess (TBG-E).⁷ Thyroxine-binding globulin deficiency leads to a decrease in protein-bound thyroid hormones in the serum, resulting in a decrease in the total T4 (Tr4) and T3 (m) levels. However, since the concentrations of free T4 (FT4) and free T3 (FT3) are not affected by the binding protein,⁸ patients with TBG deficiency have normal FT4, FT3 and thyrotropin (TSH) levels, and there is no clinical manifestation of hypothyroidism. This paper summarises and analyses the clinical characteristics of a TBG-PD patient diagnosed through genetic analysis and investigates the *Serpina7* gene mutation.

Case Description

Case Data

This study was approved by the Medical Ethics Committee of the Fourth Affiliated Hospital of Guangzhou Medical University (No. 2022-H-002).

The patient, a 26-year-old female, was hospitalised for repeated palpitations, dizziness and shortness of breath for eight months and fatigue for ten days. The patient had no obvious inducement until eight months before admission, when she began to experience palpitations and shortness of breath, combined with paroxysmal swelling, and pain and discomfort in the anterior cervical area, which were subsequently relieved. The patient visited the local hospital for treatment. The serum examination findings are shown in [Table 1](#).

A cardiac colour Doppler ultrasound examination⁹ indicated a slight prolapse of the anterior mitral valve, while the left ventricular systolic and diastolic functions were normal. Following treatment with Youjiale (50 ug qd), the symptoms of palpitations and shortness of breath were relieved, as were the swelling and pain in the neck. The patient subsequently purchased and continued to take the Youjiale (50 mg qd), and while their symptoms of palpitations and shortness of breath recurred, they were tolerable. Ten days prior to admission, the patient had no obvious inducement or symptoms such as dizziness, nausea, vomiting or headache. The patient improved on her own but presented weakness in the limbs (mainly in both lower limbs) and pain and discomfort in both knees. There was no visual acuity decline and no visual field defect. The serum examination findings are shown in [Table 1](#).

The details of the medical history of the patient were as follows:

- Previous history of fibrocystic breast disease.
- No history of hypertension.
- No history of cerebral infarction and coronary heart disease.
- No history of myocardial infarction.
- No history of atrial fibrillation.

Meanwhile, the mother had congenital heart disease and had undergone heart surgery (details unknown), while the father, brother and sister exhibited a decrease in FT3, TT3, TT4 and RT3, with the decrease in TT3 and TT4 more significant. The TBG detections across all three family members were normal at a low level and indicated a family genetic tendency.

Thyroid Function Test

Serum T3, T4, FT3, FT4 and TSH levels were determined via electrochemiluminescence (Cobas 8000, Roche Diagnostics GmbH, Switzerland), with TBG determined via chemiluminescence (DPC2000, Siemens, Germany).¹⁰ The experimental procedure was as follows: 1) preparation of standards, reagents and samples prior to the experiment; 2) sample addition (standards and samples) (100 µL), incubation at 37°C for 1 h; 3) suctioning and discarding was performed, with detection solution A (100 µL) added, followed by incubation at 37°C for 1 h; 4) plate washing was performed three times; 5) detection solution B (100 µL) was added prior to incubation at 37°C for 30 min; 6) plate

Table 1 Serum Examination Findings of Thyroid Function and Globulin Level in the Patient and the Families

	Date	TSH uIU/mL	FT3 pmol/L	FT4 pmol/L	T3 nmol/L	T4 nmol/L	rT3 ng/mL	TBG ug/mL
Proband	2020.7.25 (in local hospital)	2.33	1.62	11.39	<0.30	14.72		
	2021.3.8 (in our hospital)	2.17	1.54	11.39	<0.30	11.33		
	2021.3.28 (in our hospital)	1.490	2.03	11.81	<0.30	12.04	<0.05	14.7
	2021.6.24 (in our hospital)		1.68	13.54	0.346	12.19		
	2021.10.8 (in our hospital)	2.68	1.65	12.02	<0.30	13.73		
	2021.11.13 (in our hospital)	2.509	1.96	10.96			0.28	
Father		1.410	2.06	10.41	<0.3	13.33	<0.05	16.0
Mother		0.810	4.59	16.27	1.6	97.15	0.76	26.7
Sister		2.4	1.3	9.9	<0.3	13.66	<0.05	14.8
Brother		1.820	1.92	14.98	<0.3	18.33	<0.05	18.3
Normal range		0.3–5	2–6.6	10.3–21.0	1.8–2.9	65.0–155.0	0.2–0.8	15.0–34.0

washing was performed five times; 7) the substrate was added (100 μ L), followed by incubation at 37°C for 10 min; 8) the reading was performed. Thyroid function tests were performed on the proband and their family members.

Sequencing and Genotyping of the *Serpina7* Gene and Its Mutation

The human genomic DNA was extracted from peripheral blood leukocytes using a standard phenol-chloroform method.¹¹ The coding region of the *Serpina7* gene (exons 1–4) and exon–intron junction of the proband’s family members were directly sequenced. In addition, the coding region of the *Serpina7* gene (exons 1–4) and the exon–intron junction of 207 unrelated individuals were analysed through direct DNA sequencing and high-resolution melting (Tiangen Biotechnology Co., Ltd., Beijing, China).

Analysis Method

The patient was examined using thyroid-related antibodies and thyroid colour Doppler ultrasound, among other methods, and common thyroid diseases, such as Hashimoto’s thyroiditis, were excluded. A repeated examination of the thyroid function level showed the characteristics of a partial lack of TBG. Further gene sequencing revealed that the patient’s *Serpina7* gene locus was abnormal. Relevant literature was retrieved to analyse whether the abnormal locus was related to the decrease in TBG expression.

Literature Search

The keywords “thyroxine-binding globulin, gene and mutation” were used to search the literature in PubMed (biomedical literature database), Web of Science and other databases from their date of establishment to February 2022. A total of 45 studies were retrieved.

Results

The clinical characteristics of children with TBG deficiency and *Serpina7* gene mutation were studied. The thyroid function of the patients with TBG deficiency was tested, and genetic analysis, including in terms of family members, was conducted using polymerase chain reaction (PCR) analysis and DNA direct sequencing to detect the characteristics of TBG mutants.

Thyroid Function Test Results

The proband was a 26-year-old Chinese woman. The analysis of the venous blood indicated that the TBG (14.7 μ g/mL), T3 (<0.3 nmol/L), RT3 (<0.05 ng/mL) and T4 (14.72 nmol/L) values were lower than normal. The T3 uptake was increased, indicating that the TBG-binding affinity for T3 is affected in vitro. However, the TSH (2.33 uIU/mL), FT3 (1.62 pmol/L) and FT4 (11.39 pmol/L) levels were normal, indicating a clinically euthyroid state. These values indicate the impaired binding of T3 and, thereby, also of T4 to TBG (TBG-PD phenotype). The T3 and T4 levels in the father and younger brother significantly decreased, indicating that this phenomenon is due to a familial inherited genetic mutation. [Table 1](#) presents the test results.

Characteristics of Thyroxine Binding Globulin Mutants

The PCR amplification and direct sequencing of the target gene revealed that the patient and the father had a missense mutation in exon 4 of the *Serpina7* gene, and the nucleic acid variation was C.909(exon4)G>T. The patient was heterozygous, and the father was hemizygous. *Serpina7* C.909G(P.L303F) is a mutation and was acquired from the father through X-linked recessive inheritance ([Figure 1](#)).

Bibliography Retrieval

A total of 45 studies that met the requirements were retrieved from databases at home and abroad, with 45 articles retrieved from foreign databases and two from a Chinese database. An individual case of the *Serpina7* gene mutation with various types of mutations, including point mutation, deletion mutation, joint mutation, intron splice-site mutation

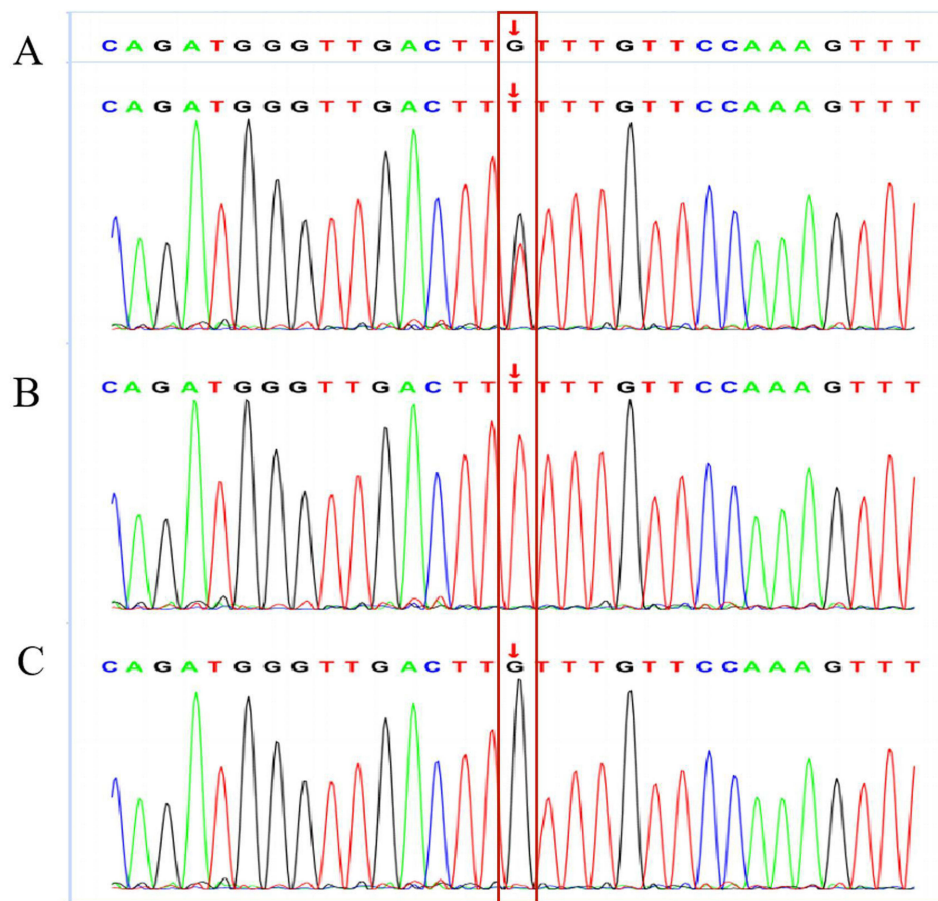


Figure 1 Characteristics of TBG mutants. (A): gene sequence of this patient; (B): gene sequence of the patient's father; (C): gene sequence of the patient's mother.

and TBG extra gene mutation was found. Except for one report of autosomal inheritance, the remainder were X-linked inheritances. Fifty-three TBG variants were identified, of which 46 were found to be mutant genes.^{2-5,11-34}

Discussion

Thyroxine binding globulin is the major thyroid hormone transport protein in the serum. Using a complementary DNA clone for the analysis of somatic cell hybrids and in-situ hybridisation, Trent et al assigned the TBG locus to Xq21-q22.³⁵ Elsewhere, Murata et al stated that the five types of inherited TBG variants have been described, all of which are X-linked. Three of these are thought to be quantitative variants and are widely distributed. It would appear that TBG is completely absent in the first form, while it appears to be physically, antigenically and functionally normal in the second and third forms. An alteration in the rate of TBG synthesis is believed to be responsible since the rates of degradation are normal.³⁶ Takamatsu and Refetoff (1986) described a sixth type of inherited TBG variant, TBG-Chicago (314200.0010), which differs from all five of the previously reported variants in being markedly resistant to heat denaturation. The other five variants have a variable degree of increased sensitivity to denaturation by heat and acid.³⁷ Takamatsu et al measured denatured TBG in sera from 32 unrelated families with inherited TBG deficiency. High levels were found in the serum samples from two out of 16 families with TBG-PD. Further studies revealed that these two families had TBG variants with alteration in both stability and isoelectric focusing patterns, thus indicating the presence of structural gene mutations.³⁸ Elsewhere, undetermined electrophoretic slow variants were found in 4% to 12% of black and Pacific Island populations, respectively.³⁹ The characteristic cathode shift of all subtypes was detected on isoelectric focusing, indicating that the difference exists in the core protein. In addition, the heat resistance of TBG-s is slightly higher, and the average undetermined human serum is low, thus reducing the T4 concentration.

The *Serpina7* gene is located in Xq22.2. The TBG deficiency caused by the *Serpina7* gene mutation is a rare thyroid disease, which is generally acquired through X-linked recessive inheritance.² The proband in this study was diagnosed with TBG-PD and was found to have a missense mutation of the *Serpina7* gene: C.909(exon4)G>T(P.L303F). The thyroid functions of her father, brother and sister indicated that the FT3, T3, T4 and RT3 levels decreased, with the decrease in T3 and T4 more substantial, which was consistent with the clinical phenotype of the patient. The TBG detection was at a normal level among all three family members. All these data indicated a family genetic tendency. Based on the nucleotide variation at this site in the human genome database, it can be concluded that the genetic variation does not belong to single nucleotide polymorphism (SNP). The amino acid sequence of the missense mutation site is relatively conservative in various species. Analyses performed using pathogenicity prediction software, such as PolyPhen-2, SIFT and Mutation Taster, indicate that the mutation will affect the protein function and has pathogenic potential. Results obtained via DynaMut server prediction indicated that the p.E91K, p.I92T and p.L303F variants reduced the protein stability, and that the p.L303F variants had a significant effect on the protein stability.¹³ The more mutation sites, the greater the impact of TBG. Fang Yanlan et al¹³ concluded that polymorphisms in the *Serpina7* gene can cause the disease, especially when multiple SNP sites are present at the same time, which can lead to decreased expression. The more SNPs carried, the lower the TBG and the higher the likelihood of complete TBG.

Therefore, it is believed that the *Serpina7* gene mutation found in the proband is the cause of the disease. In addition, the father's *Serpina7* gene's exon 4 also appeared to be a missense. As noted, the patient was heterozygous, and the father was hemizygous, meaning the gene mutation was acquired through X-linked recessive inheritance. The function of its variant protein needs to be further confirmed. The clinical manifestations of the proband in this study are completely consistent with those of TBG-PD reported in the literature.³⁴ The serum TBG, T3, RT3 and T4 values of the proband were lower than the normal values, but the TSH, FT3 and FT4 values were normal. These values are indicative of the TBG-PD phenotype. Following treatment with levothyroxine tablets, the symptoms were relieved.

Among the 16 reported TBG missense mutations, most are benign, while two are of little importance.^{38,39} The TBG-Poly mutation has no considerable effect on TBG molecules,⁴⁰ but it has a high allele frequency in different populations. The TBG mutation exhibited an X-linked genetic pattern. Most patients are hemizygous men or homozygous women. Due to the inactivation of the X chromosome, heterozygous women typically have more moderate TBG levels than both affected and unaffected men.

Studies have shown that TBG deficiency can inhibit the growth and development of bones and reduce weight.²⁹ The deficiency also leads to a decrease in thyroid hormone bound to the serum protein, but there is no clinical manifestation of hypothyroidism since the functional FT4 and FT3 concentrations are not affected by the binding protein. Therefore, normal levels of FT4 and FT3 are also an important distinguishing factor between TBG deficiency and central hypothyroidism.

This study involves certain limitations. First, the number of cases is relatively small, and while this is largely due to the rarity of the disease, the results may not be fully representative. Second, the content of the study may not be deep enough, with the lack of relevant analysis of the mechanism and function of gene mutations resulting in less abundant content. In further studies, we will adjust and deepen the study content accordingly and strive to expand the number of cases and improve the representativeness of the study.

Conclusion

The proband of this study has *Serpina7* C.909G(P. L303F), which is a mutation that was acquired from the father through X-linked recessive inheritance. The main clinical characteristics of patients with TBG deficiency are as follows: the levels of serum T4, T3 and TBG are low; the levels of TSH, FT3 and FT4 are normal; and there is no clinical manifestation of hypothyroidism. Therefore, for patients with low T4, T3 and TBG but normal TSH, the serum levels of FT3 and FT4 need to be checked in addition to the conventional consideration of central hypothyroidism. If necessary, the serum TBG level and related genes should be tested to identify TBG deficiency. This will help avoid misdiagnosis and inappropriate medical treatment and is of great significance to improving the quality of life of TBG patients.

Data Sharing Statement

All data generated or analyzed during this study are included in this article.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of The Fourth Affiliated hospital of Guangzhou Medical University (No. 2022-H-002). Written informed consent has been provided by the patient to have the case details published.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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