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Clinical recognition and evaluation of patients with inherited serum thyroid hormone binding protein mutations

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Abstract

There are three important thyroid hormone binding proteins in human serum, thyroxine-binding globulin, transthyretin and albumin. Genetic variation in these proteins can lead to altered thyroid hormone binding and abnormalities in serum tests of thyroid hormone. Importantly, patients harboring these mutations are euthyroid, thus recognition of these conditions is crucial to prevent unnecessary repeated testing and treatment. This article provides an updated overview of serum thyroid hormone transport biology and reviews the underlying genetic alterations, clinical presentation and appropriate evaluation of patients with suspected mutations in serum thyroid hormone binding proteins.

Keywords

Serum thyroid hormone binding proteins; Thyroxine binding globulin; Human serum albumin; Transthyretin; TBG deficiency; Familial dysalbuminemic hyperthyroxinemia

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Compliance with Ethical Standards

Conflict of Interest: MSM declares that her spouse receives salary and stock from Pfizer, Inc. The authors declare no competing financial interests exist.

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All procedures performed in studies involving human participants were in accordance with the ethical standards of an Institutional Review Board.

Informed Consent

Written consent was obtained in accordance with an Institutional Review Board–approved protocol.

Introduction

Thyroid hormones (iodothyronines) are important for multiple early developmental processes and metabolic regulation in adults [1]. Both the pro-hormone 3,3',5,5'-tetraiodothyronine (thyroxine, abridged as T₄), and the active form of thyroid hormone 3,3',5-triiodothyronine (triiodothyronine, abridged as T₃) are synthesized by the thyroid gland. However, T₄ is the major hormone product and in the human thyroid gland is secreted in approximately 14-fold excess compared to T₃ [2]. Supply of T₃ to extrathyroidal tissues is primarily through its generation by conversion of T₄ to T₃ and is thus regulated by local transmembrane thyroid hormone transporters and deiodinase activity in an organ- and cell-specific manner [3]. The majority of iodothyronines, including T₄, T₃ and 3,3',5'-triiodothyronine (reverse T₃, abridged as rT₃) are bound to three plasma thyroid hormone binding proteins: thyroxine binding globulin (TBG), transthyretin (TTR), and human serum albumin (HSA) [4]. In normal individuals, the relative fraction of thyroid hormone bound to a given transport protein depends primarily on its affinity for a particular iodothyronine. Thus, although HSA is the most abundant protein in the circulation, it binds only a small fraction (5–10%) of T₄ due to its relatively low affinity for iodothyronines. By comparison, TBG accounts for approximately 75%, and TTR 15–20% of T₄ binding, respectively (see Table 1 for a summary of thyroid hormone binding protein properties).

Serum thyroid hormone binding proteins function in both a hormone storage and transport capacity. In doing so, they create a physiologic buffer that prevents large fluctuations in the availability of thyroid hormone. This protects against day-to-day changes in thyroid hormone levels resulting from lack of substrate availability (e.g. due to iodine deficiency), excess urinary loss of iodine and unbound thyroid hormones, and clinical factors that affect thyroid hormone production including thyroiditis and autoimmune thyroid disease. Unbound or free T₄ represents roughly 0.03%, and free T₃ about 0.3% of the total circulating pools of T₄ and T₃, respectively [5]. Thus, greater than 99% of circulating thyroid hormone is protein-bound, allowing for retention of an abundant extra-thyroidal reserve of thyroid hormone. Additionally, because thyroid hormones are hydrophobic, binding to a carrier protein allows for transport in the circulation and uniform tissue distribution [6]. Finally, thyroid hormone binding proteins can also facilitate targeted delivery of hormones in response to physiologic requirements. For example, TBG is a member of the serine protease inhibitor (SERPIN) superfamily of proteins and is also known as SERPINA7. Similar to other SERPIN hormone transport proteins, such as cortisol binding globulin (CBG) and steroid-hormone binding globulin (SHBG), TBG retains no protease inhibitor activity. It is, however, subject to proteolytic cleavage by neutrophil elastase, which alters TBG conformation and thereby reduces its hormone binding affinity [7]. This mechanism is thought to facilitate targeted thyroid hormone delivery to sites of inflammation where neutrophil elastase is expressed.

The objective of this article is to provide a concise clinical update on genetic alterations in serum thyroid hormone binding proteins. The clinical presentation, differential diagnosis, laboratory evaluation and management of patients with mutations in serum thyroid hormone binding proteins will be reviewed.

TBG

TBG is synthesized in the liver and due to its relatively high affinity for iodothyronines, binds and carries approximately 70–75% of circulating T4 and T3. The TBG gene is located on the X-chromosome and encodes a 54 kDa protein with a mature protein of 395 amino acids [8], which post-translationally acquires four glycosyl chains [9,10]. TBG mutations, thus exhibit an X-linked inheritance pattern. Individuals with hereditary TBG deficiency have a low total T4 (TT4), total T3 (TT3) and total rT3 (TrT3), but normal free thyroid hormone levels and a normal TSH and thus are euthyroid and do not require treatment. It is important to recognize this condition to avoid inappropriate treatment for presumed hypothyroidism.

Because males have a single X-chromosome, thyroid function test (TFT) abnormalities caused by TBG variants are fully penetrant, whereas in heterozygous females, whose cells have undergone random inactivation of one X-chromosome, inherited TBG variants are variably expressed and usually produce TT4 levels that are intermediate between affected and unaffected males. Rarely, allele-selective X-inactivation of the normal TBG allele can lead to preferential expression of the mutated X-chromosome and cause a more pronounced phenotype in heterozygous females [11,12].

TBG mutations are classified based on their effect on the serum level of TBG in hemizygous males harboring the particular mutation. Specifically, mutations are designated as causing TBG complete deficiency (TBG-CD), TBG partial deficiency (TBG-PD), or TBG excess (TBG-E). Genetic mutations that cause TBG deficiency do so by producing a fraction of the protein that is devoid of function or by creating an altered protein that undergoes accelerated disposal [13–15]. Less common mutations lead to impaired TBG processing and secretion, as well as to reduced binding affinity for thyroid hormones [16,17]. Alterations that cause TBG-E are a result of gene duplication or triplication [18]. Mutant proteins secreted in serum can be visualized on gel electrophoresis by a change in band intensity that reflects increased or decreased TBG concentration (Fig. 1a, b), by a change in their migration pattern via isoelectric focusing (Fig. 1a, c) or by alteration in binding properties or stability when exposed to higher temperatures or acid [13].

TBG Complete Deficiency (TBG - CD)

TBG-CD mutations are defined as producing no detectable TBG protein. Consistent with this observation, TBG-CD mutations cause synthesis of a nonfunctional truncated protein. There have been 28 gene mutations identified and reported in the literature causing TBG-CD, all of which are large deletions, or introduce premature translation stop signals as a result of frame-shift or splice site mutations (Table 2).

TBG-CD is relatively rare with an estimated prevalence of 1:15,000 live male births [17]. TBG levels in these individuals is <5 ng/dL (0.9 mmol/L) or 0.003% that of a normal male [19]. In females heterozygous for a TBG-CD mutation, the TBG level is roughly 50% that of a normal male. Rare exceptions to this include a woman with Turner's Syndrome (XO) who was found to have a TBG-CD mutation and who was therefore fully affected [20], and

several women with 80% allele-selective X-inactivation of the normal TBG allele [12]. Theoretically, a woman homozygous for a single TBG-CD mutation or compound heterozygous for two distinct TBG-CD mutations would present similarly to an affected male, but this has not yet been described in the literature.

TBG Partial Deficiency (TBG - PD)

TBG-PD is the more common form of TBG deficiency with an estimated prevalence of 1:4,000 live births. In contrast to TBG-CD and consistent with their milder phenotype, all 18 gene variants described that cause TBG-PD are due to missense mutations (Table 2). The TBG concentration and the concentrations of TT4 and TT3 in individuals with TBG-PD are variable and depend on the specific mutation inherited. While some mutations have been shown to cause impaired protein stability [13,21] others lead to reduced binding affinity for T4 and T3 [13], and thereby cause a disproportionate decrease in levels of total T4 and T3 relative to the amount of TBG present. Other TBG mutations alter electrophoretic mobility (Fig. 1b) and/or protein stability without causing important changes in the concentration of or binding affinity for iodothyronines [22,23]. Although hemizygous males with TBG-PD exhibit mutation-specific reductions in TBG, heterozygous females often have TBG concentrations that overlap the normal range, and can be challenging to identify without genetic analysis. Notably, one variant with reduced affinity for T4 has an allele frequency of about 50% in Australian Aborigines, and was responsible for attributing a high incidence of hypothyroidism to this population [13,24], in individuals who were clinically euthyroid with normal free T4 and TSH but low total thyroid hormones. This underscores the importance of considering thyroid hormone-binding protein variants when interpreting thyroid hormone abnormalities that are inconsistent with the clinical presentation.

In addition to the mutations in the coding sequence of TBG described above, mutations in TBG regulatory domains may be associated with TBG deficiency [25]. In five percent (4/75) of families with TBG deficiency studied in our lab, sequencing of the TBG gene yielded no mutations. However, next-generation sequencing identified a single nucleotide polymorphism located in a putative liver-specific enhancer 20 kbp downstream of the coding sequence that was common to all affected individuals. Additional studies demonstrated that this polymorphism leads to reduced enhancer function *in vitro* and is likely to be important for TBG expression [25].

Challenges in TFT interpretation with TBG Deficiency

TBG deficiency should be suspected when a euthyroid individual presents with a normal TSH but a low TT4 and/or TT3. A free T4 and TBG level should be obtained for confirmation of thyroid hormone status, followed by gene sequencing. Notably, a number of cases of TBG deficiency have been reported in patients with concurrent Graves' disease. These patients exhibit a confounding pattern of TFTs with an undetectable or low TSH and low or low-normal TT4 and TT3, but elevated free thyroid hormones [26,27], reviewed in [27]. In these patients, obtaining a serum TBG level and careful assessment of clinical status can be useful in avoiding inappropriate therapy. These cases illustrate the challenges in

interpreting TFTs when thyroid hormone binding variants are present in individuals with a primary thyroid disorder.

TBG Excess (TBG-E)

Mutations that cause TBG excess are due to gene duplication or triplication resulting in TBG concentrations that are two to four times the normal range [18]. Inherited TBG-E is rare and estimated to occur in 1:25,000 live births [19]. Individuals with TBG-E have an increased TT4 and TT3 but normal free thyroid hormone levels and do not require treatment.

Acquired TBG Deficiency and Excess

A number of conditions are associated with acquired TBG deficiency including androgen excess which alters TBG glycosylation and accelerates clearance, glucocorticoid use, severe hepatocellular disease, severe non-thyroidal illness, and protein loss from severe kidney or gastrointestinal disease [28–31]. A common cause of acquired TBG excess includes increased estrogens (most commonly seen with pregnancy or oral contraceptive use), leading to increased sialylation and thus reduced clearance and a longer TBG half-life [32] (Fig 1a). These possibilities should be considered in the differential prior to evaluating for inherited TBG mutations.

TTR

TTR (also known as prealbumin or thyroxine-binding prealbumin) is a carrier for both thyroid hormones and vitamin A, thus its current name “transthyretin” which is derived from TRANSport of THYroid hormone and RETINol. TTR is located on human chromosome 18 and encodes a 55 kDa protein with a mature peptide of 127 amino acids [33]; it is a homotetramer and can bind two thyroid hormone molecules. The affinity of TTR for T4 is intermediate between TBG and HSA and it carries approximately 15–20% and 5% of circulating T4 and T3, respectively (see Table 1 and references therein).

TTR is synthesized in the liver, retina, and choroid plexus in mammals and is the predominant thyroid hormone transporter in the CSF [34]. However, studies have shown that TTR is dispensable for thyroid hormone distribution in the brain due to adaptive redundancy in the mechanisms that permit thyroid hormones to traverse the blood brain barrier [35,34]. Other studies have suggested a role for TTR in delivery of thyroid hormone to the brain during development [36] and for neural stem cell maintenance [37].

Clinical Significance of TTR Mutations

TTR mutations can lead to abnormal protein aggregation and tissue deposition and are the cause familial amyloid cardiomyopathy, familial amyloid polyneuropathy, and leptomeningeal amyloidosis. Thus, TTR mutations are broadly categorized into amyloidogenic or non-amyloidogenic variants. The timing and progression of hereditary TTR amyloidosis is variable and mutation-dependent. Affected individuals have been described with increased frequency in Portuguese, Swedish and Japanese populations [38].

Defects causing amyloidosis occur independent of TTR binding to thyroid hormones. Several TTR mutations have been identified that either increase or decrease affinity for thyroid hormones. Because TTR has a relatively low affinity for thyroid hormones compared with that of TBG, mutations that further reduce affinity do not significantly affect thyroid hormone concentrations [39]. Conversely several mutations have been described that increase affinity for T4 and rT3 (Table 3 and references therein). Individuals with these mutations show mild increases in TT4 and TrT3 levels but normal free T4 when assayed by equilibrium dialysis. These individuals are clinically euthyroid and do not require treatment. Overall, mutations in TTR are relatively rare and estimated to account for only about 2% of individuals with euthyroid hyperthyroxinemia [40].

HSA

HSA is a 66.5 kDa protein with a mature peptide comprised of 585 amino acids. It is synthesized in the liver and has many important functions including maintaining colloid osmotic pressure, and serving as a transporter and repository for both the endogenous ligands and exogenous molecules (e.g. drugs) to which it binds [41]. Albumin binds both T4 and T3, but its affinity for thyroid hormones is approximately 6,000 fold lower than that of TBG, thus HSA accounts for only 5% of T4 and 20% of T3 binding (Table 1). As a consequence of this relatively lower affinity, changes in albumin concentration do not significantly affect thyroid hormone levels, even in patients with analbuminemia [42].

Familial Dysalbuminemic Hyperthyroxinemia (FDH)

Familial dysalbuminemic hyperthyroxinemia (FDH) is an autosomal dominantly inherited condition due to gain-of-function mutations in the *HSA* gene that produce variant albumin molecules with increased affinity for thyroid hormones [43]. The prevalence of FDH is variable and depends on ethnic origin [17]. In some Hispanic populations, particularly in people of Puerto Rican descent, FDH is present in as many as 1:50 individuals [44], whereas in non-Hispanic whites the prevalence is estimated to be 1:1000 [17]. In Asians, the prevalence is somewhat lower. Notably, in Japanese individuals FDH is primarily associated with the R218P mutation that causes extreme elevation of TT4, but a relatively more modest elevation of TrT3 and a mild increase in TT3 [45–47].

Individuals with FDH are clinically euthyroid, but exhibit elevated levels of TT4, TrT3 and in some instances TT3, but have normal dialyzable free thyroid hormone levels. TSH is also normal, or non-suppressed, and patients are asymptomatic and do not require treatment. The nature and magnitude of iodothyronine elevation depends on the specific amino acid mutation in HSA. Five HSA mutations have been so far identified, four of which are located in subdomain II of the protein and primarily affect T4 binding. A fifth mutation, located in subdomain IA, primarily affects T3 binding and thus levels of TT3 are preferentially elevated [48,49].

FDH with Increased Affinity for T4 (FDH-T4)

Mutations in HSA that cause elevated TT4 affect amino acid residues arginine 218 (R218) and arginine 222 (R222), located in the binding pocket for T4. Substitution of R218 for a smaller residue is thought to electrostatically stabilize T4 interaction and thereby promotes increased binding affinity [49]. The most commonly identified albumin mutation causing FDH is R218H, which increases T4 affinity and causes a shift in migration of the HSA band on isoelectric focusing (Fig 1d). The R218H mutation results in an approximately two-fold elevation in TT4, but relatively little change in TT3 and a very mild increase in TrT3. It is common in Hispanics and is linked to a polymorphism in exon 13, suggesting a common ancestral origin [50]. R218S has been described in only one family of Bangladeshi origin and has an intermediate effect on binding, causing an approximately nine-fold increase in TT4, minimal change in TT3 and a two- to three-fold increase in TrT3 [51]. R218P, identified in a Japanese and a Swiss family, causes a greater than 1000-fold increase in T4 affinity and thus leads to the greatest degree of elevation in TT4 (approximately 17-fold). TT3 may be normal or up to two-fold elevated, and TrT3 is increased six-fold in these patients [52,47]. Finally, R222I, identified in three Somali families and an individual from Croatia, leads to a 40- to 70-fold increase in TrT3 but to only an approximately two-fold increase in TT4 and minimal increase TT3 [53] (see Table 4 for a summary of average changes in TFT levels in individuals with FDH).

FDH with Increased T3 Affinity (FDH-T3)

The L66P mutation is located in subdomain IA of the HSA protein, which is predicted to be important for T3 binding [49]. It was first described in a Thai infant that presented with isolated elevated TT3. Interestingly, her TT3 and TT4 levels were repeatedly found to be low by analog methods, leading to unnecessary treatment with thyroid hormone despite being asymptomatic [48]. TT3 levels were later determined to be elevated when evaluated by radioimmunoassay using the labeled native T3, underscoring the importance of using non-analog methods for determining thyroid hormone levels in these cases.

FDH Clinical Considerations

FDH is the most common inherited cause of euthyroid hyperthyroxinemia and should be considered in patients with a normal TSH, who are found to have elevated thyroid hormone levels, especially when inconsistent with clinical symptoms and signs. Diagnosis is suggested by the presence of a similar pattern of lab abnormalities in family members and should be confirmed by sequencing of the albumin gene. A similar pattern of TFTs may be seen in acute non-thyroidal illness, including psychosis [54], interference by the presence of endogenous heterophile antibodies (e.g. Human Anti-mouse Antibodies, Rheumatoid Factors) [55] or biotin supplementation [56], TSH-oma [57], resistance to thyroid hormone beta RTH β [58], or use of certain common medications, thus these conditions are included in the differential diagnosis (Table 5). However, in the presence of heterophile antibodies, TSH-oma, or RTH β , free thyroid hormone levels are also expected to be elevated. And, in the latter two conditions, patients may be symptomatic [58,57]. Notably, in patients with FDH, the free T4 and free T3 levels are notoriously elevated when measured by automated

indirect assays that rely on antibody-conjugated T4 analogs with variable affinity for the mutant albumin [59]. Additionally, high concentrations of chloride, as seen in some commercial free T4 assays, can inhibit T4 binding to albumin, and inaccurately estimate free T4 in patients with HSA [59]. Thus when evaluating for FDH, it is recommended to obtain a free T4 by equilibrium dialysis, with T4 measured by liquid chromatography coupled with tandem mass spectroscopy. Diagnosis of FDH is important to avoid inappropriate treatment of euthyroid individuals with abnormal lab tests.

Other Albumin Mutations

Many HSA variants have been identified, most of which are clinically and biologically silent and have no effect on thyroid hormone binding. These variants are referred to as alloalbumin and bisalbumin, named for their alternate banding patterns on gel electrophoresis. These variants produce either a stable or transient band that migrates to a different location from the wild-type albumin protein or a double band in heterozygous individuals [60]. Alloalbumin and bisalbumin variants do not cause significant changes in thyroid function tests. Similarly, individuals with analbuminemia, or the complete lack of albumin, present with fatigue, mild edema and cholesterol abnormalities but do not have significant thyroid test abnormalities [60,47].

Conclusions

Defects in serum thyroid hormone binding proteins should be suspected when the clinical presentation does not support the results of the thyroid function tests. Patients with TBG deficiency or excess exhibit reduced or increased levels of total T4, T3 and rT3, respectively, but normal levels of free thyroid hormones. Many individuals with TTR mutations develop inherited amyloidosis, but do not have abnormalities in serum thyroid hormone levels due to the relatively low affinity of TTR for thyroid hormones. A minority of TTR mutations cause increased affinity for thyroid hormones. Patients with these mutations exhibit euthyroid hyperthyroxinemia but do not have amyloidosis. As is the case with TTR, individuals with HSA mutations that reduce thyroid hormone binding affinity have thyroid function tests that are indistinguishable from those of unaffected individuals. Mutations that increase thyroid hormone binding affinity for HSA cause FDH and these individuals exhibit euthyroid hyperthyroxinemia or, more rarely euthyroid hypertriiodothyroninemia, are asymptomatic and do not require treatment. It is important to recognize these conditions to avoid unnecessary diagnostic testing and therapy, especially given that most direct measurements of free T4 yield falsely elevated results.

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Fig. 1.

Isoelectric focusing (IEF) gels demonstrating microheterogeneity of TBG and HSA variants with (a) increased estrogen levels in pregnancy (b) TBG-Glencoe a mutation causing TBG-PD, (c) TBG-S, a mutation causing altered TBG migration (d) HSA R218H, the most common mutation causing FDH. Tracer amounts of ^{125}I were added to serum prior to separation on a gel by isoelectric focusing and autoradiography. The isoelectric point is the pH at which a particular molecule carries no net electrical charge. (a) In pregnancy, increased estrogen levels increase sialylation producing an anodal shift of TBG bands due to the added negative charge from the increase in sialic acid. (b) TBG-PD causes reduced concentration of TBG but no change in isoelectric point. (c) In TBG-S, Asp 171 is replaced by Asn, leading to loss of a negative charge, and resulting in slower migration by IEF. Serum from a heterozygous female expressing both WT TBG and TBG-S shows a mixed pattern (lane 1), serum from a hemizygous male shows only the mutant band (lane 2). (d) Substitution of Arginine 218 with Histidine in HSA causes an anodal shift in the migration pattern in mutants.

Abbreviations: TBG WT = TBG wildtype, TBG+E = TBG with increased estrogen, TBG-PD = TBG Partial Deficiency, TBG-S = TBG Slow, HSA = Human serum albumin.

Table 1.

Properties of the three major serum thyroid hormone binding proteins (for references see [17])

		TBG	TTR	HSA
Association Constant, K_a (M^{-1})	T4	1×10^{10}	2×10^8 *	1.5×10^6 *
	T3	1×10^9	1×10^6	2×10^5
Percent bound	T4	75	20	5
	T3	75	<5	20
Serum Concentration (mg/L)		16	250	40,000
Half-life (days)		5	2	15

* Value is given for the high-affinity binding site only

Table 2.

TBG Variants and Gene Mutations (for references see [17])

TBG NAME	Abbreviated name	Intron Exon	CODON ^I	AMINO ACID		NUCLEOTIDE	
				WT	Variant	WT	Variant
Complete Deficiency (CD)							
Milano (fam A)	CDMi ²	<i>int 1</i>	<i>fs</i>	5' DSS	unknown	gtaagt	gttaagt
Andrews	CDAN	<i>int 1</i>	<i>fs</i>	5' DSS	unknown	gtaagt	gcaagt
Portuguese 1 (pt A)	CDP1	1	23	S (Ser)	X (OCH)	TCA	TAA
Yonago	CDY	1	28–29 ~~fs~~ -51	D F	X (OPA)	GA(CT)TT	GAATT
Negev (Bedouin)	CDN	1	38 ~~fs~~ -51	T (Thr)	X (OPA)	ACT	T del
Nikita (fam B)	CDNi	1	50 ~~fs~~ -51	P (Pro)	X (OPA)	CCT	T del
Taiwanese 1	CDT1 ²	1	52	S (Ser)	N (Asn)	AGC	AAC
Parana	CDPa ²	1	61	S (Ser)	C (Cys)	TCC	TGC
Miami	CDMia	1	64 ~~fs~~ -106	A (Ala)	X (AMB)	GCC	G del
No name	CD6	1	165 ~~fs~~ -168	V (Val)	X (OCH)	GTT	T del
Kankakee	CDK	<i>int 2</i>	188 ~~fs~~ -195	3' ASS	X (OPA)	agCC	ggCC
Poland	CDPL	2	201 ~~fs~~ -206	D (Asp)	X (OCH)	GAC	G del
Portuguese 2 (pt B)	CDP2	2	223	Q (Gln)	X (OCH)	CAA	TAA
No name	CD5 ²	2	227	L(Leu)	P (Pro)	CTA	CCA
Portuguese 3 ³	CDP3	2	233	N (Asn)	I (Ile)	ACC	ATC
Berlin	CDBn	<i>int 3 +3</i>	279~~fs~~-324	–28 bp	X (OPA)	TTG A	TGA
Houston	CDH	<i>int 3</i>	279 ~~fs~~ -374	3' ASS	X (OPA)	agAT	aaAT
Buffalo	CDB	3	280	W(Trp)	X (AMB)	TGG	TAG
Taiwanese 2	CDT2	3	280	W(Trp)	X (OPA)	TGG	TGA
Lisle	CDL	<i>int 4</i>	280 ~~fs~~ -325	5' DSS	X (OPA)	gtaaa	ggaaa
Jackson (fam K)	CDJa	<i>int 4</i>	280 ~~fs~~ -325	5' DSS	X (OPA)	gtaaa	gtaag
No name	CD7	3	283 ~~fs~~ -301	L(Leu)	X (OPA)	TGT	G del
No name	CD8 ²	4	329 ~~fs~~ -374	A (Ala)	X (OPA)	GCT	G del
Japan	CDJ	4	352 ~~fs~~ -374	L(Leu)	X (OPA)	CTT	C del
Penapolis	CDPe	4	332 ~~fs~~ -374	K(Lys)	X (OPA)	AAG	A del
Kyoto ³	CDKo	4	370	S (Ser)	F (Phe)	TCT	TTT
Harwichport	CDH	4	381 ~~fs~~ -396	Y (Tyr)	X (OPA)	AGG	19 nt del
Neulsenburg	CDNI	4	384 ~~fs~~ -402	L(Leu)	7 aa add	CTC	TC del
Partial Deficiency (PD)							
Allentown	PDAT	1	–2	H (His)	Y (Tyr)	CAC	TAC
San Diego	PDSD ²	1	23	S (Ser)	T (Thr)	TCA	ACA
Brasilia	PDB	1	35	R (Arg)	W(Trp)	CGG	TGG

TBG NAME	Abbreviated name	Intron Exon	CODON ¹	AMINO ACID		NUCLEOTIDE	
				WT	Variant	WT	Variant
Wanne-Eickel ⁴	PDWE	1	35	R (Arg)	E (Glu)	CGG	CAG
Mainz 1 ⁶	PDMZ1	1	52	S (Ser)	R (Arg)	AGT	AGA
Mainz 2 ⁶	PDMZ2	1	64	A (Ala)	D (Asp)	GCC	GAC
Korea ⁵	PDKa	1	74	E (Glu)	K(Lys)	GAG	AAG
Gary	PDG	1	96	I (Ile)	N (Asn)	ATC	AAC
Mainz 3 ⁷	PDMZ3	1	112	N (Asn)	L(Lys)	AAT	AAG
Montréal	PDM	1	113	A (Ala)	P (Pro)	GCC	CCC
Aborigine	PDA ²	2	191	A (Ala)	T (Thr)	GCA	ACA
Glencoe	PDGe	2	215	V (Val)	G (Gly)	GTG	GGG
Quebec	PDQ ²	4	331	H (His)	Y (Tyr)	CAT	TAT
Japan (Kumamoto)	PDJ	4	363	P (Pro)	L(Leu)	CCT	CTT
Heidelberg	PDHg	4	368	D (Asp)	G (Gly)	GAT	GGT
Mainz 4 ⁶	PDMZ4	4	381	R (Arg)	G (Gly)	AGG	GGG
Mainz 5 ⁶	PDMZ5	4	382	S (Ser)	R (Arg)	AGT	CGT
No name		<i>enhancer</i>	-	-	-	G	A
Other Variants							
Slow	S	1	171	D (Asp)	N (Asn)	GAC	AAC
Polymorphism	Poly	3	283	L(Leu)	F (Phe)	TTG	TTT
Chicago	CH or Cgo	3	309	Y (Tyr)	F (Phe)	TAT	TTT

¹ Codon numbering is from the first amino acid of the mature protein. The 20 amino acids of the signal peptide are numbered -1 to -20, from C- to N-terminus. For frame shift mutations, the codon at the site of mutation is followed by the codon at the site of termination of translation.

² Coexistence of TBG Poly.

³ Complete deficiency is uncertain as the TBG assay used was unable to detect values <10% the mean normal.

⁴ Moeller LC, Vinzelberg P, Jaeger A, Appiyagyei-Dankah Y, Fingerhut A, Mann K, Janssen OE. Two novel mutations leading to partial and complete thyroxine-binding globulin deficiency. Symposium of the German Society for Endocrinology, March 7–11 2007, Salzburg, Austria.

⁵ Also a silent mutation at codon 55: GCA→GCG.

⁶ Personal communication Joachim Pohlenz, Universitätsmedizin Mainz, Germany.

Abbreviations: aa, amino acid; add, addition; del, deletion; fs, frame shift; pt, patent; fam, family; int, intron; ASS, acceptor splice site; DSS, donor splice site; N/A, not applicable; OCH, ochre stop codon, OPA, opal stop codon, AMB, amber stop codon.

Table 3.

TTR variants with altered affinity for T4 and potentially an effect on TFTs

RELATIVE AFFINITY FOR T4 (Mutant / Normal)		CODON	AMINO ACID		NUCLEOTIDE		REF
			WT	Variant	WT	Variant	
HOMOZYGOUS	HETEROZYGOUS						
DECREASED AFFINITY							
<0.1	0.17 – 0.41	30	V (Val)	M (Met)	GTG	ATG	[61,39]
ND	0.54	58	L (Leu)	H (His)	CTC	CAC	[39]
ND	0.45	77	S (Ser)	Y (Tyr)	TCT	TAT	[39]
ND	0.19 – 0.46	84	I (Ile)	S (Ser)	ATC	AGC	[61,39]
0.3 – 0.62	1.0	122	V (Val)	I (Ile)	GTC	ATC	[62,39]
NEUTRAL							
ND	1.0	49	T (Thr)	A (Ala)	ACC	GCC	[62]
0	0.7	55	L (Leu)	P(Pro)	CTG	CCG	[62]
ND	~1.0	60	T (Thr)	A (Ala)	ACT	GCT	[61,39]
ND	0.7	68	I (Ile)	L (Leu)	ATA	TTA	[62]
ND	1.1	71	V (Val)	A (Ala)	GTG	GCG	[62]
ND	0.9	102	P (Pro)	R (Arg)	CCC	CGC	[62]
0.29	0.7	111	L (Leu)	M (Met)	CTG	ATG	[62]
INCREASED AFFINITY							
ND	3.5 [†]	6	G (Gly)	S (Ser)	GGT	AGT	[39]
8.3–9.8	3.2 – 4.1	109	A (Ala)	T (Thr)	GCC	ACC	[39,63]
ND	7.2	109	A (Ala)	V (Val)	GCC	GTC	[64]
ND	~2.0	119	T (Thr)	M (Met)	ACG	ATG	[65]

[†] Probably overestimated since the subjects harboring this TTR variant have normal serum TT4 concentrations.

Table 4.

Effect of HSA mutations on serum thyroid hormone levels

	Average Fold-change in Thyroid Hormone Levels				
HSA Mutation	TSH	Total T4 (µg/dL)	Total T3 (ng/dL)	RT3 (ng/dL)	Reference
L66P	Normal	1.1	3.3	1.0	[48]
R218H	Normal	2.0	1.2	1.5	[50]
R218S	Normal	8.8	1.3	2.6	[51]
R218P	Normal	16.8	1.9	6.1	[52,47]
R222I	Normal	2.6	1.2	86.0	[53]

Table 5.

Differential diagnosis of thyroid hormone abnormalities exhibiting elevated T4 and/or T3 and non-suppressed TSH

Etiology	Thyroid Function Tests	Clinical Presentation	Additional Evaluation
Acute non-thyroidal illness and psychosis	• TSH variable • TT4 and FT4 elevated	• Concurrent illness, psychosis	• TrT3 usually elevated
Assay interference (e.g. heterophile antibodies, biotin supplement)	• TSH variable • TT4 and FT4 variable	• Asymptomatic, euthyroid	• Heterophile Abs elevated (e.g. HAMA, RF) • Normalization following holding biotin $\times$ 48–72 hours
TSH-oma	• TSH normal or slightly elevated • TT4, FT4, TT3 elevated	• Clinically hyperthyroid	• Alpha subunit may be elevated • Family members normal
RTHβ	• TSH normal or slightly elevated • TT4, FT4 and often TT3 elevated	• Clinical signs of hyperthyroidism are variable • Common findings include goiter, hyperactivity, tachycardia	• <i>THRB</i> gene sequencing • Family members also affected • Positive response to TRH stimulation and/or • T3 suppression
Medications: Amiodarone	• Transient TSH elevation • FT4 elevated, TT3 normal due to inhibition of DIO1	• Asymptomatic, euthyroid	
Medications: Heparin	• TSH normal • TT4, FT4, TT3 elevated	• Asymptomatic, euthyroid	• Exacerbated by hypoalbuminemia, hypertriglyceridemia
Medications: Thyroid hormone replacement with variable adherence	• TSH elevated • TT4, FT4, TT3 variable	• History of autoimmune hypothyroidism	

Abbreviations: HAMA, Human anti-mouse antibodies; RF, Rheumatoid Factor; RTH β , Resistance to Thyroid Hormone β ; DIO1, iodothyronine deiodinase 1.