A Novel Mutation in the *Albumin* Gene (R218S) Causing Familial Dysalbuminemic Hyperthyroxinemia in a Family of Bangladeshi Extraction

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Background: Familial dysalbuminemic hyperthyroxinemia (FDH) is a common cause of euthyroid hyperthyroxinemia. Clinical recognition of FDH is crucial for preventing unnecessary therapy in clinically euthyroid patients with abnormal thyroid function tests. Our goal was to identify the cause of abnormal serum tests of thyroid function in a Canadian family of Bangladeshi extraction.

Patients: The probanda was found to have elevated free thyroxine (fT4) and free triiodothyronine (fT3) with nonsuppressed thyrotropin (TSH) on screening blood work. After detailed studies excluding hyperthyroidism and resistance to thyroid hormone, blood was obtained from all members of her immediate family for further investigation.

Methods: We conducted laboratory analyses and sequencing of candidate genes.

Results: Two members of this family have FDH, caused by a not previously identified mutation in the *albumin* gene. This mutation, located in exon 7 of the gene (652A>C), produces a single amino acid substitution in the protein molecule (R218S). The mutant albumin is associated with a ninefold increase in serum total T4 and a twofold increase in serum total reverse T3 compared to patients with normal albumin. Modeling data for the R218S variant are compatible with the increased binding affinity of this variant albumin for T4.

Conclusions: The R218S substitution reported here causes FDH that, in terms of the magnitude of serum triiodothyronine elevation, is intermediate to the two previously reported mutations at codon 218 FDH: R218H being more mild and R218P more severe.

Introduction

FAMILIAL DYSALBUMINEMIC HYPERTHYROXINEMIA (FDH) is an autosomal dominant condition producing euthyroid hyperthyroxinemia. The findings in the most common form include an elevation of serum total thyroxine (TT4), total reverse triiodothyronine (TrT3), and, to a lesser extent, serum total T3 (TT3) (1). Patients with FDH (2,3), like those with other conditions caused by functional abnormalities in thyroid hormone binding proteins (1), can present to a variable extent with falsely elevated free T4 (fT4) when measured by routine direct methods, leading to the erroneous diagnosis of hyperthyroidism. This can result in inappropriate surgical and chemical therapy (4).

Fifteen years elapsed between the first description by Hennemann *et al.* (5) and Lee *et al.* (6) in 1979 and the independent identification by Sunthornthepvarakul *et al.* (7) and

Petersen *et al.* (8) in 1994 of the *albumin* (*ALB*) gene mutation resulting in the replacement of the normal arginine 218 with a histidine (R218H). This mutant albumin protein has a relatively modest increase in the affinity for T4 and to a lesser degree for T3 (7), as indicated by the magnitude of serum TT4 elevation in euthyroid individuals (9). In 1997, Wada *et al.* (10) identified another mutation at the same codon producing replacement of the arginine with a proline (R218P). This variant albumin molecule had markedly increased affinity for T4, producing on average a 17-fold increase of serum TT4 concentrations compared to the twofold increase of the R218H variant (10,11). In 1998, Sunthornthepvarakul *et al.* (12) identified another gain-of-function *ALB* gene mutation in a Thai family, replacing the normal leucine 66 with a proline (L66P). This mutant albumin has higher affinity for T3 and produces a predominant elevation of TT3, with a negligible increase in TT4. This variant is referred to as FDH-T3.

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Here we present a novel mutation in the *ALB* gene, found in a Canadian family of Bangladeshi extraction. The mutation replaces the normal arginine 218 with a serine (R218S). Serum TT4 concentrations were approximately ninefold the mean normal value, compared to a twofold increase in subjects with R218H (1). The albumin molecule presented herein is associated with serum thyroid test abnormalities intermediate to those of albumin R218H and R218P.

Patients and Methods

Patients

The probanda is the second child born to unrelated parents of Bangladeshi parents living in Canada. She came to the attention of one of us (ESN) at the age of 21, after routine screening revealed a high serum fT4 with a normal thyrotropin (TSH). Repeat testing revealed fT4 values ranging from 1.90 to 2.11 ng/dL (reference range 0.71–1.85 ng/dL) using the Abbott Architect i2000, and 6.45 and 7.54 ng/dL (reference range 0.86–1.71 ng/dL) using the Roche e601 Cobas 6000. fT3 values ranged from 0.48 to 0.67 ng/dL (reference range 0.16–0.37 ng/dL) on the Abbott Architect i2000, and 0.70 and 0.79 ng/dL (reference range 0.26–0.44 ng/dL) using the Cobas 6000. Corresponding TSH values were 0.74–1.2 mU/L (reference range 0.30–5.0 mU/L) on both platforms. The presence of a TSH-secreting pituitary adenoma was ruled out by normal levels of the TSH alpha subunit and absence of a pituitary adenoma on nuclear magnetic resonance, supported by clinical euthyroidism. These findings initially suggested a diagnosis of resistance to thyroid hormone (RTH), but sequencing of the *thyroid hormone receptor beta* (*THRB*) gene showed no abnormalities. There was neither goiter nor tachycardia, both commonly seen in RTH (13). The probanda is a university student.

Similar abnormalities in thyroid function tests were found in the probanda's mother: serum TSH values ranging from 3.4 to 4.5 mU/L, fT3 of 0.40 and 0.53 ng/dL on the Abbott Architect i2000 and Cobas 6000 respectively, and fT4 of 0.75 and 4.12 ng/dL on the Abbott Architect i2000 and Cobas 6000 respectively. fT4 was >6.0 ng/dL (reference range 0.57–1.63 ng/dL) on the Beckman DXI platform. She is asymptomatic, a university graduate, and a banker.

To evaluate for the presence of RTH without a *THRB* gene mutation, the responses to graded doses of LT3 were measured in the probanda, using a standard protocol (13). Serum TSH suppressed normally to values of 0.05 and 0.03 mU/L on the last two doses (100 and 200 µg/dL) of LT3. TSH response to TRH was not measured because TRH is no longer available in North America.

In a search to explain these unusual findings, blood samples of the probanda and immediate family members were sent to the University of Chicago for further study after obtaining written consent for a study protocol approved by the Institutional Review Board. At the time of blood sampling, the probanda was using hormonal contraceptives, and her father was taking glimepiride, metformin, insulin, rosuvastatin, ramipril, furosemide, and bisoprolol. No family member was taking supplements containing biotin, which is known to interfere with platforms that use biotin and avidin (14). All subjects were asymptomatic.

Tests of thyroid function

Serum TSH, TT4, TT3, TrT3, and thyroglobulin (TG) concentrations were measured as described previously (11). Iodothyronine measurements used both the Elecsys and Immulite platforms as well as liquid chromatography followed by tandem mass spectrometry (LC/MS/MS) (see supplemental data in reference (15)). fT4 was measured by equilibrium dialysis (Quest Diagnostics, San Juan Capistrano, CA) (16).

Isoelectric focusing

Isoelectric focusing (IEF) was performed on Phastgel (GE Healthcare, Pittsburgh, PA), pH 4–6.5. Undiluted sera were first incubated for two hours at room temperature with 1.6 µmol/L LT4 to reduce the binding of radiolabeled T4 to thyroxine-binding globulin (TBG) and transthyretin (TTR). Sera were then incubated with 15,000 cpm [¹²⁵I]T4 for 30 minutes. One µL of each serum/T4 mixture was applied to the Phastgel and subjected to electrophoresis for 400 volt-hours on a PhastSystem (Pittsburgh, PA). After electrophoresis, the gel was dried and [¹²⁵I]T4-bound proteins were visualized by autoradiography.

DNA sequencing

DNA was extracted from white blood cells using the QIAamp DNA Blood Mini Kit (Qiagen, Valencia, CA). The *ALB* gene, exons 7–10 of the *THRB* gene, and all coding regions of the *TSHR* gene (encoding the TSH receptor) were amplified and sequenced on a 3730XL DNA Analyzer (Applied Biosystems, Inc., Carlsbad, CA). Primers and reaction conditions have been reported previously (11,17).

Results

Thyroid function tests and IEF (Fig. 1)

The probanda (II-2) and her mother (I-2) have elevated TT4 and TrT3. To confirm the accuracy of high TT4 values, measurements were repeated after ethanol extraction and dilution with T4-deficient serum on two platforms: Elecsys and Immulite and by LC/MS/MS. The authenticity of the TT4 was confirmed (Table 1). Although both the probanda and her mother have the same *ALB* gene mutation causing FDH (see below), TT3, TT4, and TrT3 were increased to a higher degree in the probanda. This is a consequence of estrogen in the hormonal contraceptive used by the probanda, which increases the TBG concentration and thus the serum binding capacity for all iodothyronines. The estrogen effect on TBG is clearly seen by the anodal shift of the TBG isoforms on IEF as previously described (18). T4 measured by equilibrium dialysis (fT4D) was within normal range in all family members. Serum TSH was slightly elevated in the probanda, as well as in her unaffected sister (II-1) and father (I-1).

IEF showed an anodal shift of the albumin band (FDH albumin, Fig. 1) in both individuals with the high serum TT4 and TrT3.

Identification of the *ALB* gene mutation and sequencing of the *TSHR* gene

Sequencing of the *ALB* gene of the probanda (II-2) and her mother (I-2) revealed a C to A transversion in exon 7 (652C>A; Fig. 1). This substitution predicts replacement of

TABLE 1. MEASUREMENTS OF TOTAL THYROXINE (TT4; $\mu\text{g/dL}$) BY DIFFERENT METHODS

Subject	Relationship	Immunometric assays			Ethanol extract ^a
		Immulite	Elecsys	LC/MS/MS	
I-1	Father	6.9	7.2	5.8 (80)	6.6
I-2	Mother	66	70	52 (74)	64
II-1	Sister	9.6	9.1	6.8 (75)	9.3
II-2	Proband	81	85	62 (73)	79

^aNormal recovery range 70–80%.

LC/MS/MS, liquid chromatography followed by tandem mass spectrometry.

the normal arginine 218 (CGC) with a serine (AGC; R218S). Because serum TSH concentrations were in the upper limit of the reference range in three family members, and slightly above the reference range in one individual (I-1), the *TSHR* gene was sequenced but no abnormalities were found (data not shown).

Discussion

Defects in serum thyroid hormone transport proteins can lead to alterations in the concentrations of serum iodothyronines.

These abnormalities affect the total rather than free concentrations of iodothyronines in serum. TBG accounts for approximately 75% of bound T3 and T4, and excess or deficiency of this protein can directly alter the measured concentrations of both iodothyronines (1). TTR is responsible for 20% of bound T4 and less than 5% of T3. As expected, gain of function mutations of the *TTR* gene tend to increase serum T4 but not T3 (1). Albumin accounts for the remaining 5% of bound T4 and 20% of T3. Because of its relatively minor role in thyroid hormone transport, albumin deficiency is usually

FIG. 1. Pedigree of the family showing the genotypes with thyroid function tests, isoelectric focusing (IEF) findings, and chromatograms. All results are aligned with the symbols on the pedigree. Iodothyronines were measured on the Elecsys platform. Corresponding total thyroxine (TT4) values measured by LC/MS/MS are in Table 1 and those of total triiodothyronine (TT3) are 125, 115, 261, and 160 ng/dL for I-1, II-1, II-2, and I-2 respectively. Abnormal values are in bolded numbers. The probanda is indicated with an arrow. Mut, mutant. Note the anodal shift of the albumin band (FDH albumin) in subjects with the *ALB* gene mutations. The anodal shift of all TBG bands of the probanda (II-2) is due to an estrogen-induced increase in sialylation of TBG (18).

clinically silent to endocrinologists (19). Mutations that increase the affinity for iodothyronines, as in FDH, result in variable increases in TT4, TT3, and TrT3, depending on the properties of the mutant albumin.

Here, we report a new *ALB* gene mutation that causes FDH. The probanda was asymptomatic when a routine screen revealed elevated serum fT4 and fT3 levels with non-suppressed TSH. As workup ruled out a TSH-secreting pituitary adenoma and, subsequently, a similar pattern was observed in her mother who was also asymptomatic, the possibility of RTH was considered. Both clinical and genetic investigations were negative. Further analysis confirmed that the probanda and her mother have FDH. They share a previously unreported mutation of the *ALB* gene (652C>A), producing the substitution R218S. This mutation causes higher TT4 than R218H but lower than R218P (Table 1). The anodal shift of the mutant albumin on IEF suggests loss of a basic amino acid in the variant molecule, as predicted by the genomic sequence. This is consistent with IEF results of other albumin mutations causing FDH (11,20). Both individuals were clinically euthyroid, like most other families with mutations at position 218 (7,10,21).

Borderline high TSH concentrations were found in all four family members. The relative magnitude did not correlate with the albumin defect. As there was no clinical (goiter) or laboratory (antibodies) evidence of autoimmune thyroid disease in any of the four subjects, nor iodine deficiency, the *TSHR* gene was sequenced, but no abnormalities were found. We have no explanation for the borderline hyperthyrotropinemia.

Mutations of R218, located within subdomain IIA of the human serum albumin, enhance the affinity for T4, resulting in the elevation of the levels of this iodothyronine associated with FDH. Structural data for human serum albumin in complex with T4 (22) revealed that residues W214, R218, and R222 are also involved in the binding of T4. The conformation of T4 in this binding site is *cisoid*, placing the phenolic ring and the amino-propionic acid side chain on the

TABLE 2. THE EFFECT OF *ALB* VARIANTS WITH INCREASED AFFINITIES FOR IODOTHYRONINES ON IODOTHYRONINE CONCENTRATIONS IN SERUM

	TT4 ($\mu\text{g/dL}$)	TT3 (ng/dL)	TrT3 (ng/dL)	n
WT	8.0 ± 0.2	125 ± 4	22.5 ± 0.9	83
R218H	16.0 ± 0.5 (2.0)	154 ± 3 (1.2)	33.1 ± 1.1 (1.5)	84
R218S (This report)	70 (8.8)	159 (1.3)	55.7 (2.6)	1
R218P	135 ± 17 (16.8)	241 ± 25 (1.9)	136 ± 13 (6.1)	8
L66P	8.1 ± 0.6 (1.0)	326 ± 21 (2.6)	22.3 ± 0.9 (1.0)	6

Values reported are means $\pm$ standard error, and the number of subjects per genotype are under "n." Note that for ALB R218S, only one subject is listed, as the second subject with the same defect also had elevated TBG due to estrogen-containing contraception. Numbers in parentheses indicate the fold above the mean normal value for the WT ALB R218. All data were generated in the Chicago laboratory except for four of the eight individuals with ALB R218P.

same side of the tyrosyl ring (23) as a result of steric interactions with W214, R218, and R222.

Structural data for the R218H and R218P variants of albumin showed that these substitutions have smaller volumes than R218, and result in a relaxation of steric restrictions on thyroxine binding at this site (22). As noted by these authors, and reported by Petersen *et al.* (24), a smaller side chain at position 218 affords additional space within the triad of W214-H218(P218)-R222 for hormone binding. The smallest, A218, has the highest affinity for T4. There are also concerted rotations of the side chains along the helix incorporating the variant R218H that creates additional space for ligand binding. The anomalous ranking of the affinity of R218P variant as deduced from the serum TT4 concentrations (9) (see Table 2) can be explained as a result of the larger distortion of the helix conformation compared to the smaller adjustments

FIG. 2. (A) Crystal structure of the human serum albumin-T4 complex (22) showing the T4-binding environment of subdomain IIA with the side chains of R218, R222, and T214 (green). (B) The crystal structure, modeled in pink, is that of the mutant R218S with hydroxyl side chain. (C) The relative sizes of the amino acid side chains at position 218 for the wild type R; variants P, H, and S; and the recombinant A with the highest affinity for T4 (24). Color images available online at www.liebertpub.com/thy

observed for R218H. These moderate conformational adjustments apparently are sufficient to increase binding affinity by at least an order of magnitude.

If one accepts the greater distortions in the helix for the R218P variant as the cause for its anomalously higher binding affinity for T₄, then the observed ninefold increase in TT₄ for the R218S variant reported here (Table 2) is in line with the pattern observed for R218H. Modeling data for the R218S variant also show that the hydroxyl of S218 is within hydrogen bonding distance (3.0 Å) to the backbone carbonyl of W214 (Fig. 2).

It is known that standard direct (antibody-based) assays for fT₄ and fT₃ produce erroneously high values in patients with FDH (2). This was the case in the subjects reported herein. However, the values were much higher in the Cobas 6000 and Beckman platforms than the Abbott Architect i2000, as previously reported (3). All three systems accurately measured the elevated TT₄, which was confirmed by ethanol precipitation of the serum proteins and extraction of the iodothyronines as well as by LC/MS/MS (Table 1). Given proprietary restraints, the reason for the dramatic differences in the fT₄ values obtained using the different platforms is difficult to investigate. However, the buffer used may play an important role (9). The fact that three of the known mutations causing FDH are located at codon 218 is not due to the presence of a CpG, as only one of the three, namely R218H, can be ascribed to post-transcriptional methylation and demethylation.

Clinical recognition of FDH is important primarily because of the risks of misdiagnosis. The prevalence of FDH caused by ALB R218H is estimated at 1 in 100 individuals of Hispanic origin (25). Patients are likely to be suspected of having hyperthyroidism or RTH if tested by standard, direct methods of fT₄ measurement (11), and may be subjected to unnecessary, and potentially irreversible, treatment.

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Author Disclosure Statement

S.M.G., A.M.F., E.S.N., A.M.D., and R.E.W. have nothing to declare. S.R. is academic associate for Quest Diagnostic Laboratories and is therefore considered a consultant.

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