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# THYROID HORMONE PATTERNS IN FAMILIAL DYSALBUMINEMIC HYPERTHYROXINEMIA (R218H MUTATION) IN DIFFERENT ASSAY PLATFORMS

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## Introduction

- Familial dysalbuminemic hyperthyroxinemia (FDH) is an autosomal dominant condition characterized by artefactual hyperthyroxinemia as a result of enhanced binding affinity of thyroid hormones to the mutant albumin.
- The commonest form of FDH is due to a missense amino acid change, replacing arginine at codon 218 with histidine (R218H)<sup>1</sup>
- FDH R218H mutation results in normal thyroid stimulating hormone (TSH) reflecting a euthyroid state but elevated total T4.
- Measurement of free thyroid hormone by equilibrium dialysis is reportedly normal but measurements across many current commercial assay platforms return artefactually high Free T4 levels. As a result, potential for misdiagnosis arises and patients may be treated unnecessarily.
- The effect of FDH on Free T3 assays is less well known.

## Aim

- To determine how performance of commercially available Free T4 and Free T3 assays are affected

## Methods

- We included 37 patients, all of whom had a confirmed heterozygous mutation (R218H) in the *ALB* gene. Patients with a concomitant thyroid disorder (identified by abnormal TSH level) were excluded.
- In all patients TSH, Free T4, Free T3, TBG and total T4 were measured.
- **Free T4 & Free T3 measurements:**
- **2-Step methods**
  - Wallac DELFIA: Perkin Elmer
  - Architect c800: Abbott Ltd Diagnostics
  - Access: Beckman Coulter
- **1-Step methods**
  - ADVIA Centaur XP®: Siemens Medical Solutions Diagnostics
  - ELECSYS E170: Roche Diagnostics
  - Vitros Eci : Ortho Clinical Diagnostics, Johnson & Johnson, Beersse, Belgium)
- Total T4 was measured by the DELFIA *PerkinElmer* method.
- Thyroid-binding globulin (TBG) was measured by Siemens Immulite 2000

## Results

Table 1. % of FDH R218H patients with measured Free T4 and Free T3 levels above reference range for all platforms

% Patients with thyroid hormone above RR	Delfia: Perkin Elmer	Architect c800: Abbott Beckman Coulter	Access: Beckman Coulter	Advia Centaur XP: Siemens	Elecsys E170: Roche	Vitros Eci: Ortho
Free T4 (%)	45.9	42.1	100	83.8	91.9	0
Free T3 (%)	13.8	13.5	-	29.8	18.9	-

1. **Total T4** levels were above upper limit of normal (141nmol/L) for all patients (Range 159-300nmol/L)

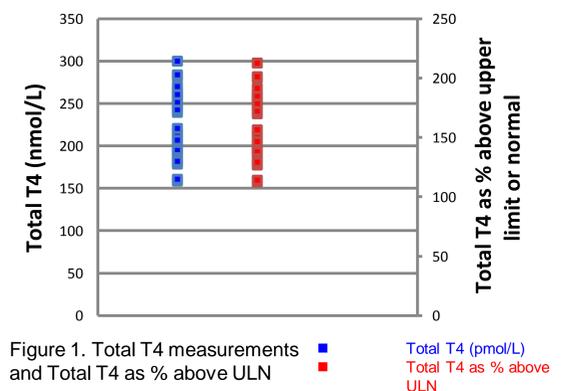


Figure 1. Total T4 measurements and Total T4 as % above ULN

2. **Free T4** levels were raised in majority of the platforms (Fig. 2). Free T4 levels were all above the upper limit measured with ACCESS: Beckman Coulter assay and with VITROS were normal to low.
3. **Free T3** levels were raised in the 4 tested platforms (Fig. 3) with as high as 29.8% of patients returning high Free T3 when assayed with Advia Centaur (Table 1)

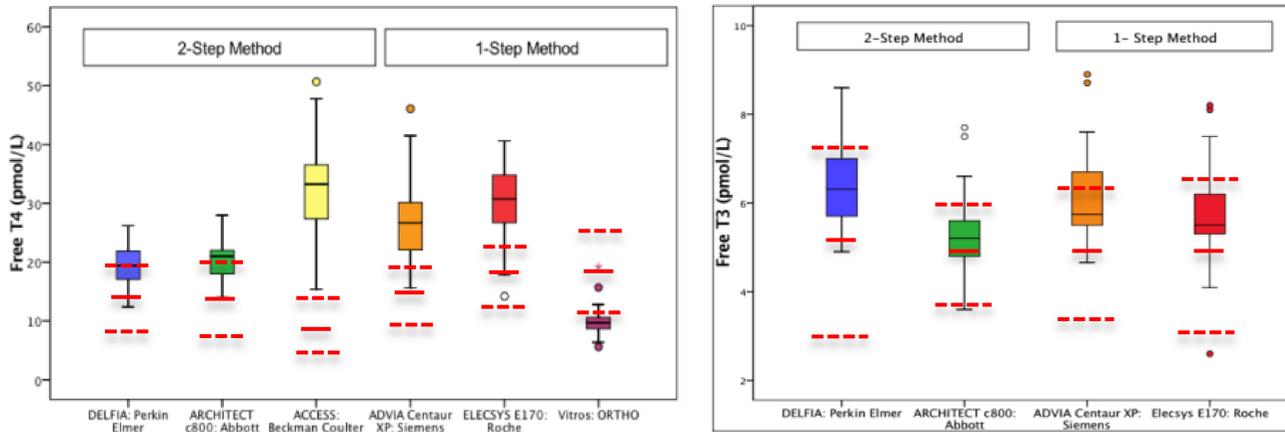


Figure 2. & Figure 3. Free T4 and Free T3 levels measured in FDH (R218H) patients across all platforms. — in box indicates median values and whiskers min and max range, --- Indicates limits of reference ranges and — mean value provided by manufacturer except Vitros. Reference range and mean for Vitros based on Erasmus MC reference ranges

- Free T4 measurements were variably raised but sometimes falsely normal in first degree relatives of probands who were found to have genetically-proven FDH.
- Total T4 levels are all raised in all family members

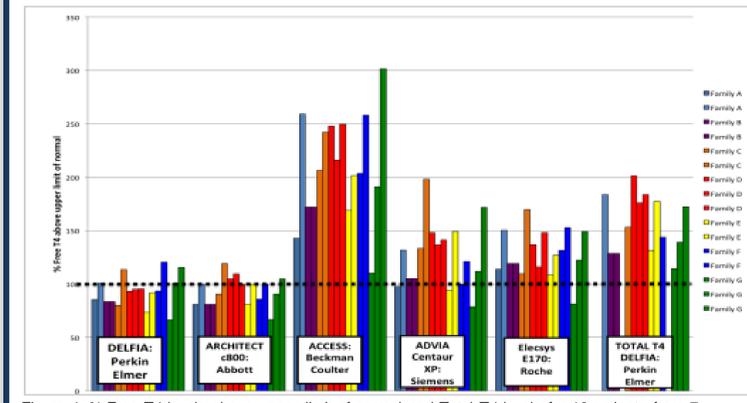


Figure 4. % Free T4 levels above upper limit of normal and Total T4 levels for 16 patients from 7 unrelated families across all platforms. Each bar represents one individual and each family represented by a different colour

## Discussion & Conclusions

- All commercially available Free T4 assays were affected by FDH, but to variable extents.
- Notably, the Beckman assay returns very raised Free T4 results, with other assays returning lesser elevations of Free T4, and the Vitros assay returning normal- low Free T4 levels. The reason for such differences is not known, but has been suggested to be due to differing assay buffer compositions<sup>2</sup>.
- Free T3 assays are also affected by FDH, but to a lesser degree.

- In clinical practice, the erroneous attribution of a raised FT4, FT3 with normal TSH to Resistance to Thyroid Hormone beta or a TSH secreting pituitary tumour could lead to unnecessary investigation and treatment.
- The variability in measured Free T4 levels between R218H FDH family members may reflect the assay used and the HPT axis setpoint in each individual.
- In a clinically euthyroid individual with normal TSH and elevated thyroid hormone levels, consideration and investigation for assay interference (either genetic or acquired) is the most appropriate first step.



Reference:

1. Sunthornthepvarakul T, Angkeow P, Weiss RE, Hayashi Y, Refetoff S. An Identical Missense Mutation in the Albumin Gene Results in Familial Dysalbuminemic Hyperthyroxinemia in Eight Unrelated Families. Vol. 202, Biochemical and Biophysical Research Communications. 1994, p. 781–7.
2. Ross HA, de Rijke YB, Sweep FC. Spuriously high free thyroxine values in familial dysalbuminemic hyperthyroxinemia. Clin Chem. 2011 Mar;57(3):524-5



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Thyroid

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Poster presented at:

