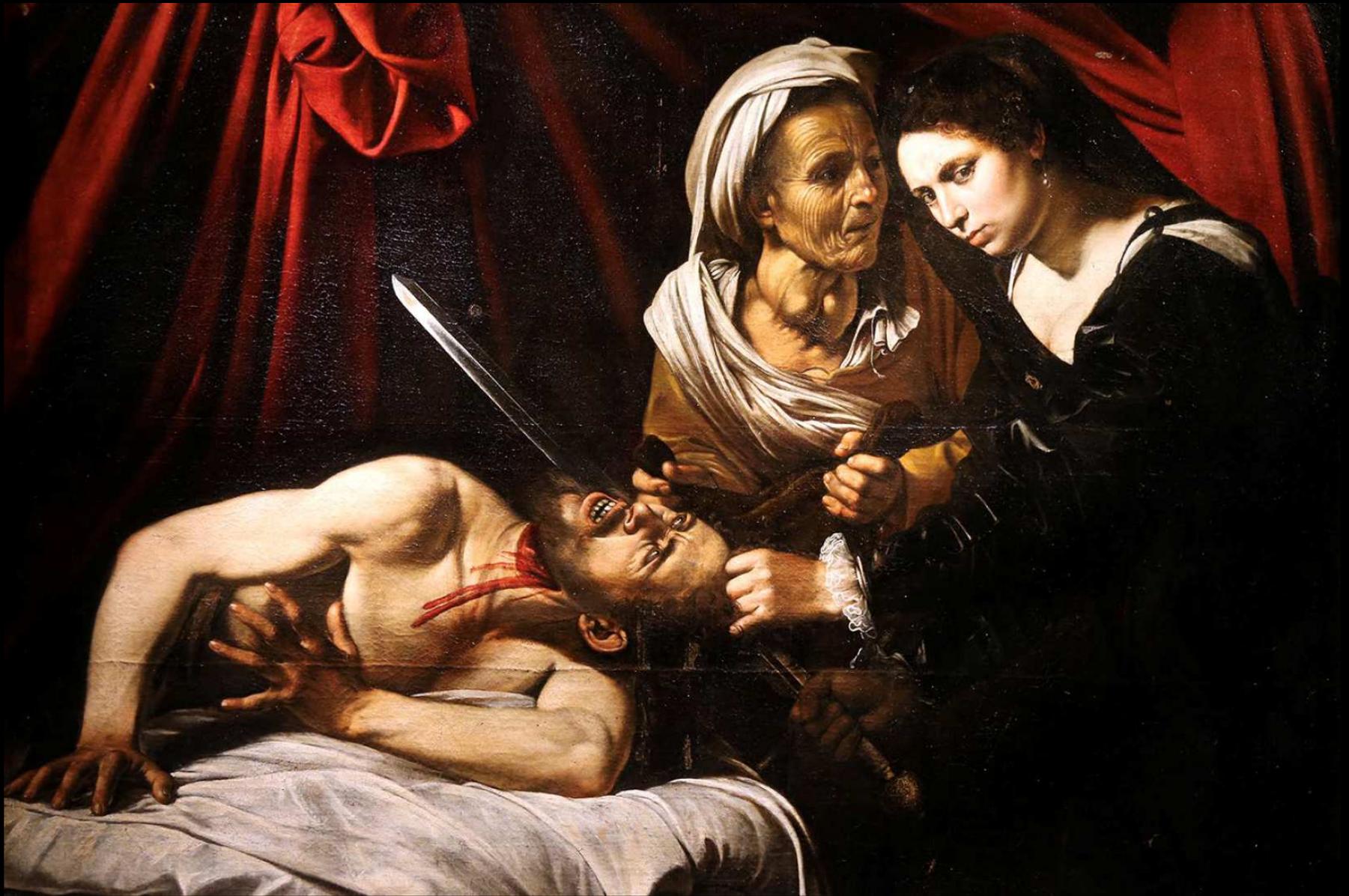


**FRIDAY THE 13TH
IS STILL BETTER
THAN MONDAY
THE WHATEVER.**

Freitagskonferenz | 13. Juli 2018

Matthias Hepprich





Michelangelo Merisi (1571-1610) | Die Enthauptung des Holofernes

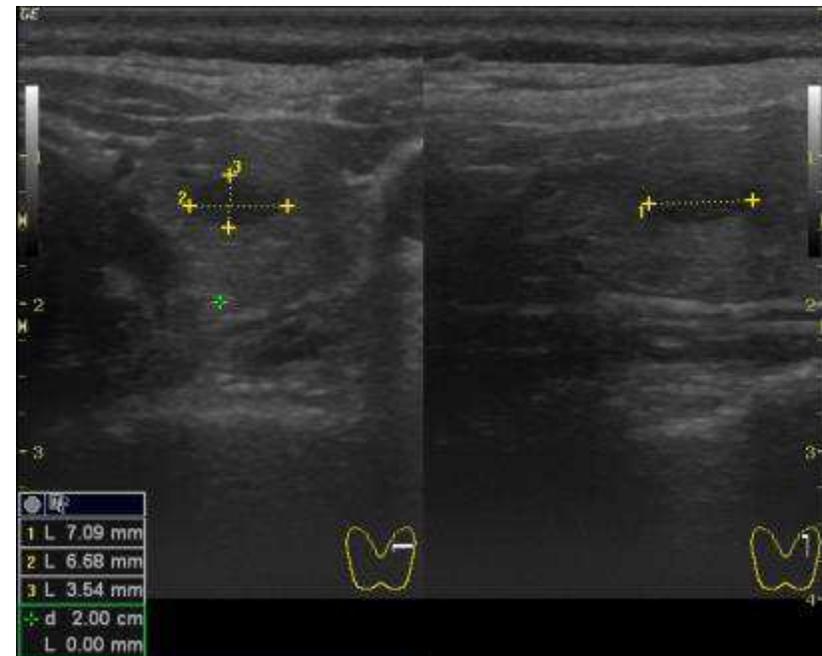
Traversari M et al. J Endocrinol Invest (2016) 39:1203–1204

Kasus Frau T. S., Jg. 1960

- Zuweisung zur Nachsorge bei St. n. Isthmusknoten-Resektion (Ø 2.4 cm) bei Struma multinodosa (Bethesda IV) und unklar erhöhten freien SD-Hormonwerten
 - Adenom
- **PA:** Menopause ca. 50-jährig, St. n. transientem Hemisyndrom rechts (kardioembolisch bei PFO), Verschluss mittels Schirm 2000
- **FA:** Hypercholesterinämie, Vater (Pneumonie), Mutter unklar verstorben, Cousine ms Mamma-Ca 48-jährig verstorben, keine SD-Erkrankungen bekannt
- **SA:** KV-Angestellte, allein lebend, keine Kinder
- **Status:** Grösse 179 cm, Gewicht 78 kg, BMI 24.3 kg/m², BD 137/76 mmHg, HF 78/min, regelmässig, Schilddrüse indolent, schluckverschieblich ohne Knotenbildung palpabel, keine zervikale Lymphadenopathie

Sonografie Schilddrüse

- Struma multinodosa, SD-Volumen 19.5 ml



Labor

	unit	04/2006	12/2016	02/2017
TSH	mIU/l	1.73	1.93	1.99
fT4	pmol/l	28.4	25.7	29.1
fT3	pmol/l	nd	8.6	8.2

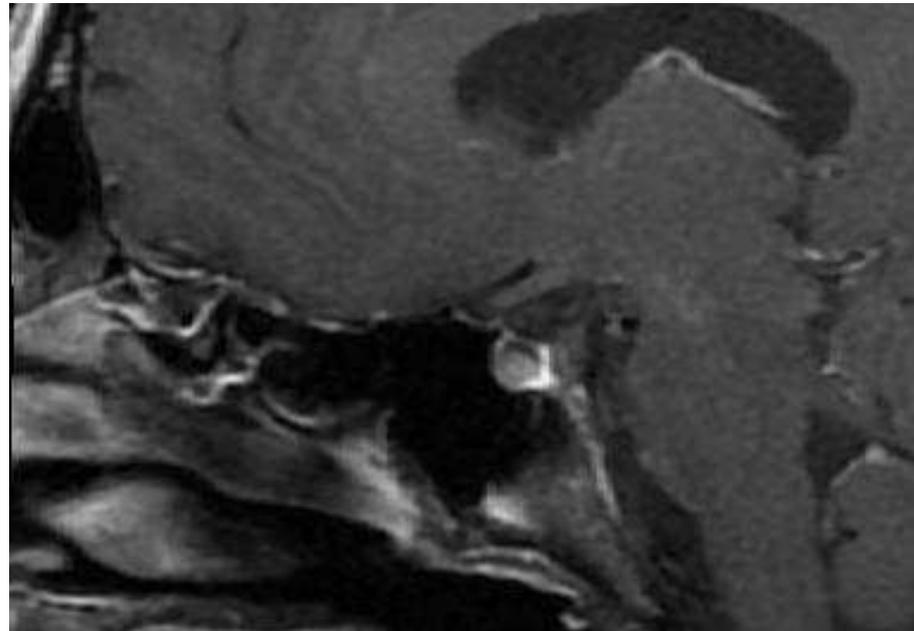
reference
0.332-4.490
11.6-22.0
2.6-5.6

- Blutbild, Chemogramm bland

	unit	04/2017	reference
Prolaktin	mIU/l	211	102-496
IGF1	nmol/l	23.3	6.1-30.8
Cortisol	nmol/l	477	80-683
LH	IU/l	53.9	7.7-58.5
FSH	IU/l	64.8	25.8-135.0
Oestradiol	pmol/l	<18.4	<18.4-505

MRI-Sella

- T2w, gering hypointense, glatt berandete, gegenüber umstehendem Hypophysengewebe leicht vermindert KM-aufnehmende 4x5 mm durchmessende Läsion der Adenohypophyse dorsal paramedian rechts



Verlauf

	unit	04/2006	12/2016	02/2017	04/2017	reference
TSH	mIU/l	1.73	1.93	1.99	2.86	0.332-4.490
fT4	pmol/l	28.4	25.7	29.1	37.0	11.6-22.0
fT3	pmol/l	nd	8.6	8.2	11.2	2.6-5.6
total T4	nmol/l	nd	nd	116	140	66-181
total T3	nmol/l	nd	nd	2.3	3.1	1.2-3.2

Resistance to thyroid hormone is associated with raised energy expenditure, muscle mitochondrial uncoupling, and hyperphagia

Catherine S. Mitchell,¹ David B. Savage,¹ Sylvie Dufour,² Nadia Schoenmakers,¹ Peter Murgatroyd,¹ Douglas Befroy,³ David Halsall,⁴ Samantha Northcott,¹ Philippa Raymond-Barker,¹ Suzanne Curran,¹ Elana Henning,¹ Julia Keogh,¹ Penny Owen,⁵ John Lazarus,⁵ Douglas L. Rothman,⁶ I. Sadaf Farooqi,¹ Gerald I. Shulman,^{2,3,7} Krishna Chatterjee,¹ and Kitt Falk Petersen³

¹University of Cambridge Metabolic Research Laboratories, Institute of Metabolic Science, Addenbrooke's Hospital, Cambridge, United Kingdom.

²Howard Hughes Medical Institute and ³Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut.

⁴Department of Clinical Biochemistry, Addenbrooke's Hospital. ⁵Department of Medicine, University of Cardiff, United Kingdom.

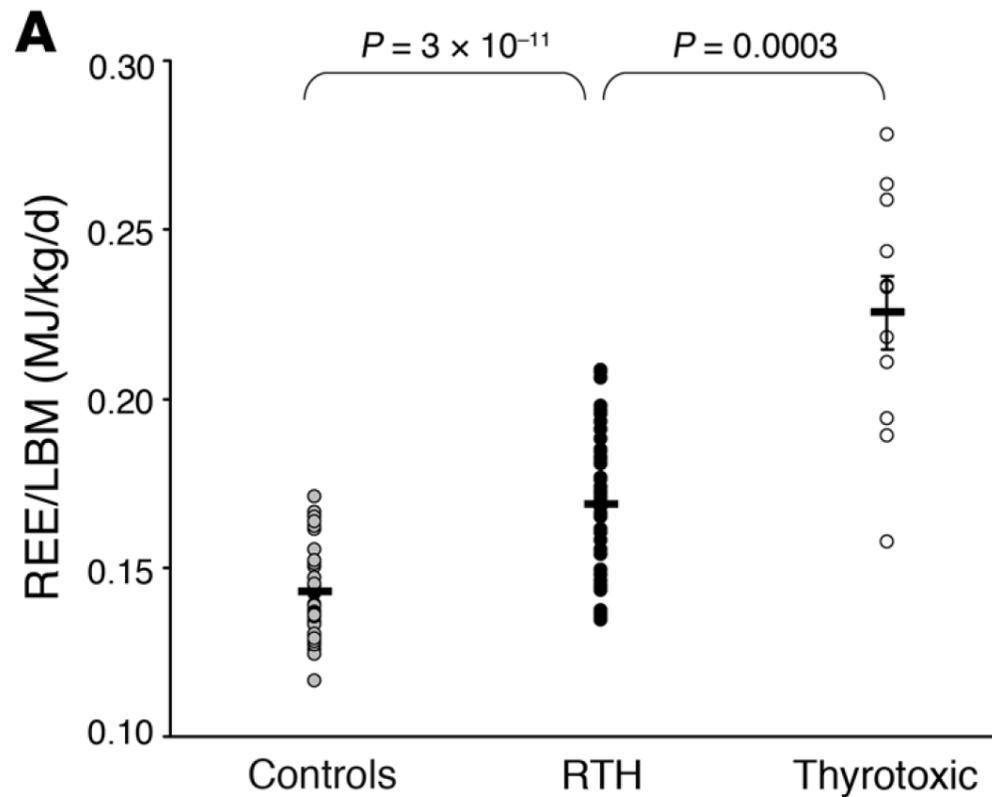
⁶Department of Diagnostic Radiology and ⁷Department of Cellular and Molecular Physiology, Yale University School of Medicine.

Metabolische Charakterisierung von RTH-Patienten

	Control (16 M, 29 F)	RTH (22 M, 32 F)	Thyrotoxic (3 M, 8 F)	ANOVA <i>P</i> value	<i>P</i> value (RTH vs. control)	<i>P</i> value (RTH vs. thyrotoxic)
Age (yr)	37.5 ± 1.7	40.6 ± 2.0	44.1 ± 4.2	0.25	NS	NS
Weight (kg)	69.3 ± 2.1	71.9 ± 2.0	64.8 ± 2.7	0.27	NS	NS
BMI (18.5–25 kg/m ²)	24.5 ± 0.7	26.2 ± 0.7	23.7 ± 0.8	0.10	NS	NS
Fat to lean mass ratio	0.49 ± 0.04	0.60 ± 0.04	0.61 ± 0.06	0.06	<0.05	NS
TSH (0.4–4.0 mU/l)	1.56 ± 0.12	4.06 ± 0.56	<0.03	<0.01	<0.01	<0.01
fT4 (9–20 pmol/l)	13.7 ± 0.3	33.7 ± 1.6	38.9 ± 6.7	<0.01	<0.01	NS
fT3 (3–7.5 pmol/l)	5.5 ± 0.1	13.3 ± 0.6	25.8 ± 3.2	<0.01	<0.01	<0.01
Sleeping heart rate (bpm)	60 ± 1	67 ± 1	79 ± 4	<0.01	<0.01	<0.01
HOMA-IR (1.0)	1.3 ± 0.2	1.9 ± 0.2	1.2 ± 0.1	0.02	<0.05	NS
FFA (280–920 μmol/l)	268 ± 18	359 ± 21	479 ± 47	<0.01	<0.01	<0.05
Total cholesterol (mmol/l)	4.7 ± 0.2	4.8 ± 0.1	4.1 ± 0.3	0.10	NS	NS
LDL cholesterol (mmol/l)	2.8 ± 0.1	3.0 ± 0.1	2.5 ± 0.2	0.13	NS	NS
Triglycerides (mmol/l)	1.2 ± 0.1	1.5 ± 0.1	1.0 ± 0.1	0.11	NS	NS
HDL cholesterol (mmol/l)	1.5 ± 0.1	1.2 ± 0.1	1.2 ± 0.1	<0.05	0.01	NS
SHBG	48.1 ± 4.0	34.1 ± 3.1	129.6 ± 15.4	<0.01	<0.01	<0.01

Data were analyzed using ANOVA with post-hoc Dunnett's analyses. *P* values of less than 0.05 were considered significantly. The number 1.0 for HOMA-IR is based on the assumption that normal-weight, healthy subjects aged less than 35 years have an insulin resistance of 1 and β cell function of 100%. M, male; F, female.

Ruheenergieumsatz erhöht bei RTH und Thyreotoxikose



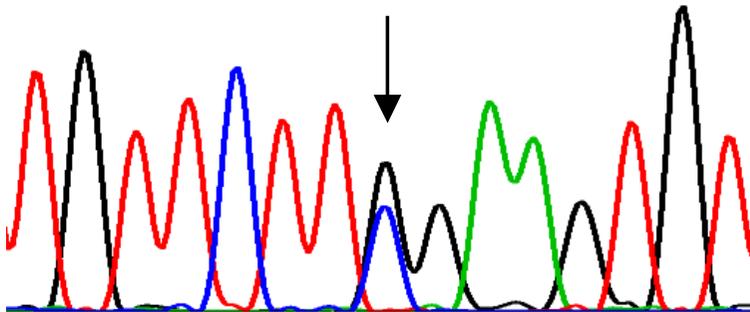
REE 15% höher (1625 kcal/d) im Vgl. zur Referenz 1447 kcal/d (Mifflin-Formel)

Genetische Sequenzierung

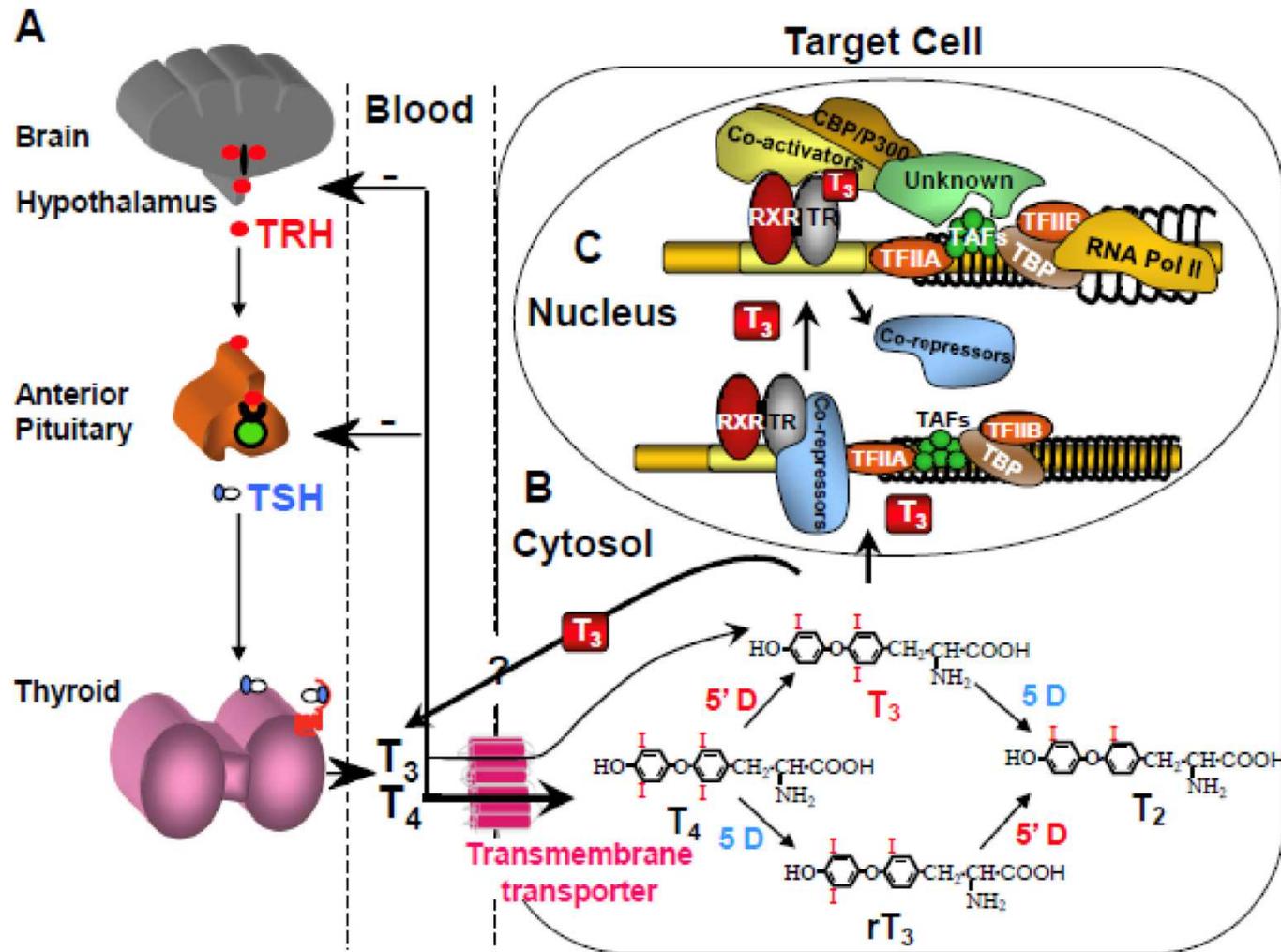
- Exon 10 nicht beschriebene heterozygote Mutation *THRB*
- Leucin → Phenylalanin
- CADD-Score: 23

THRB: c.1368G>C p.(L456F)

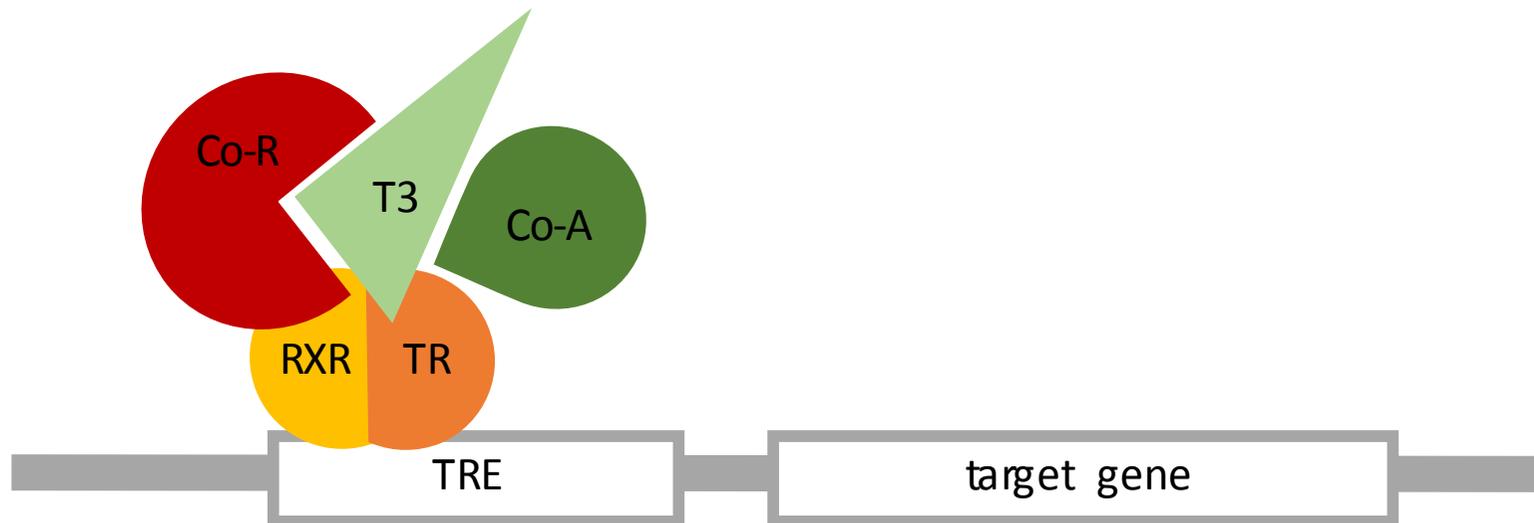
T G T T C T T S G A A G T G T



Thyroid hormone regulation



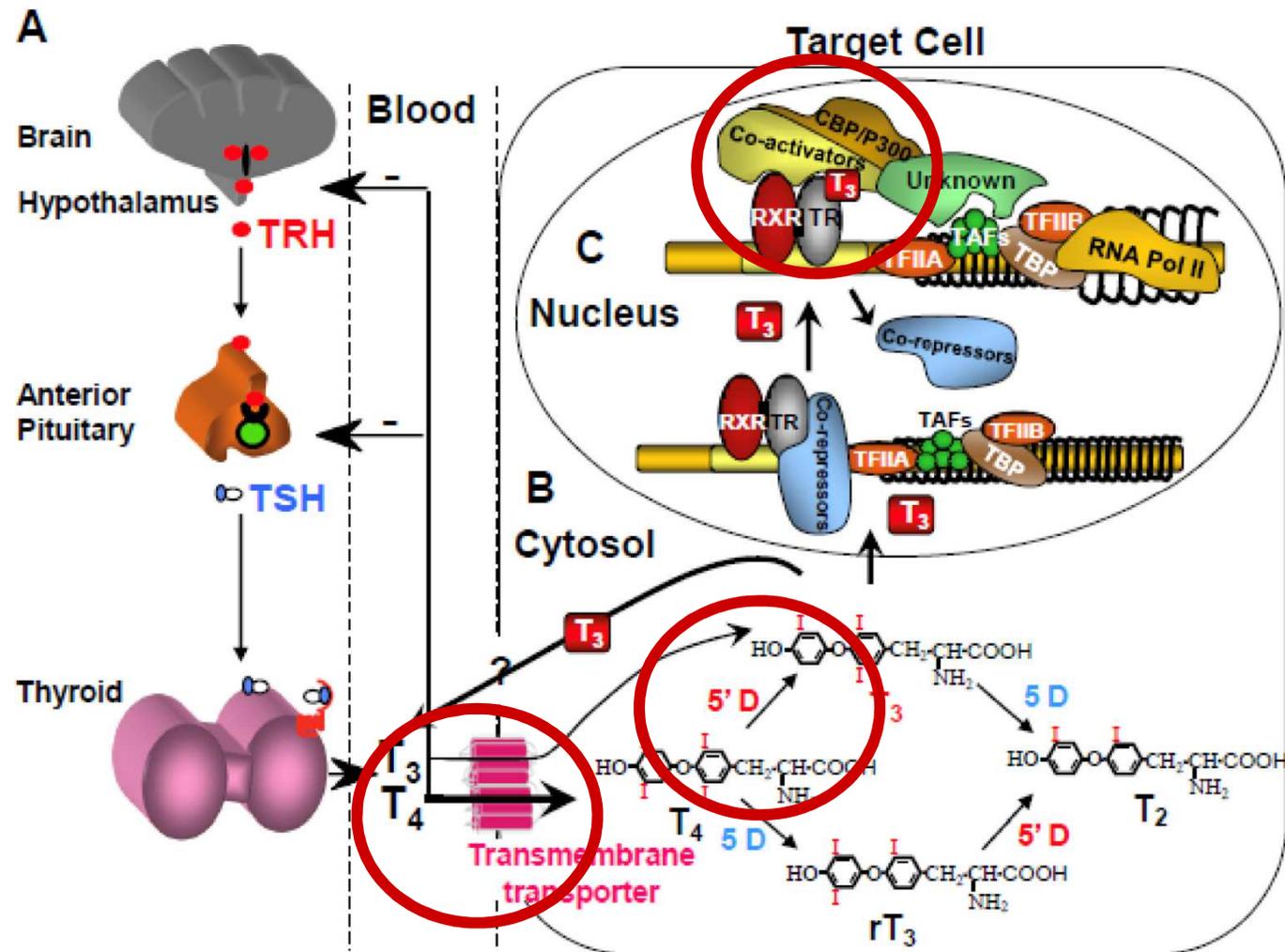
Nuclear action of T3



Thyroid hormone receptors

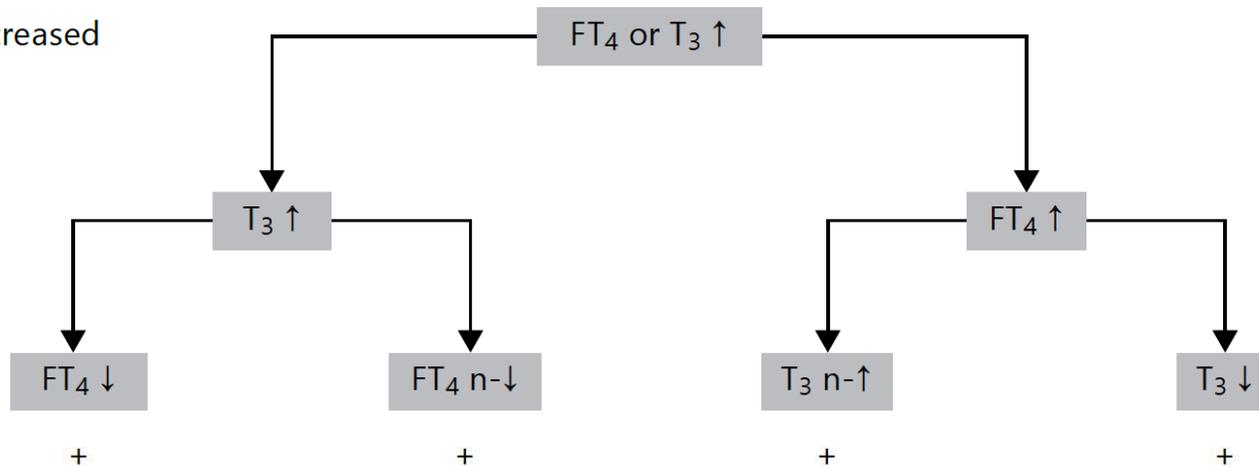
Receptors	Thyroid hormone receptors			
	TR α		TR β	
Isoforms	TR α_1	TR α_2	TR β_1	TR β_2
T ₃ binding	yes	no	yes	yes
Functionality	functional	nonfunctional	functional	functional
Highest expression	myocardium skeletal muscle intestine bone CNS		liver kidney	hypothalamus pituitary gland inner ear retina

Thyroid hormone action defects (THAD)



Thyroid hormone action defects (THAD)

(A) Predominantly increased thyroid hormone



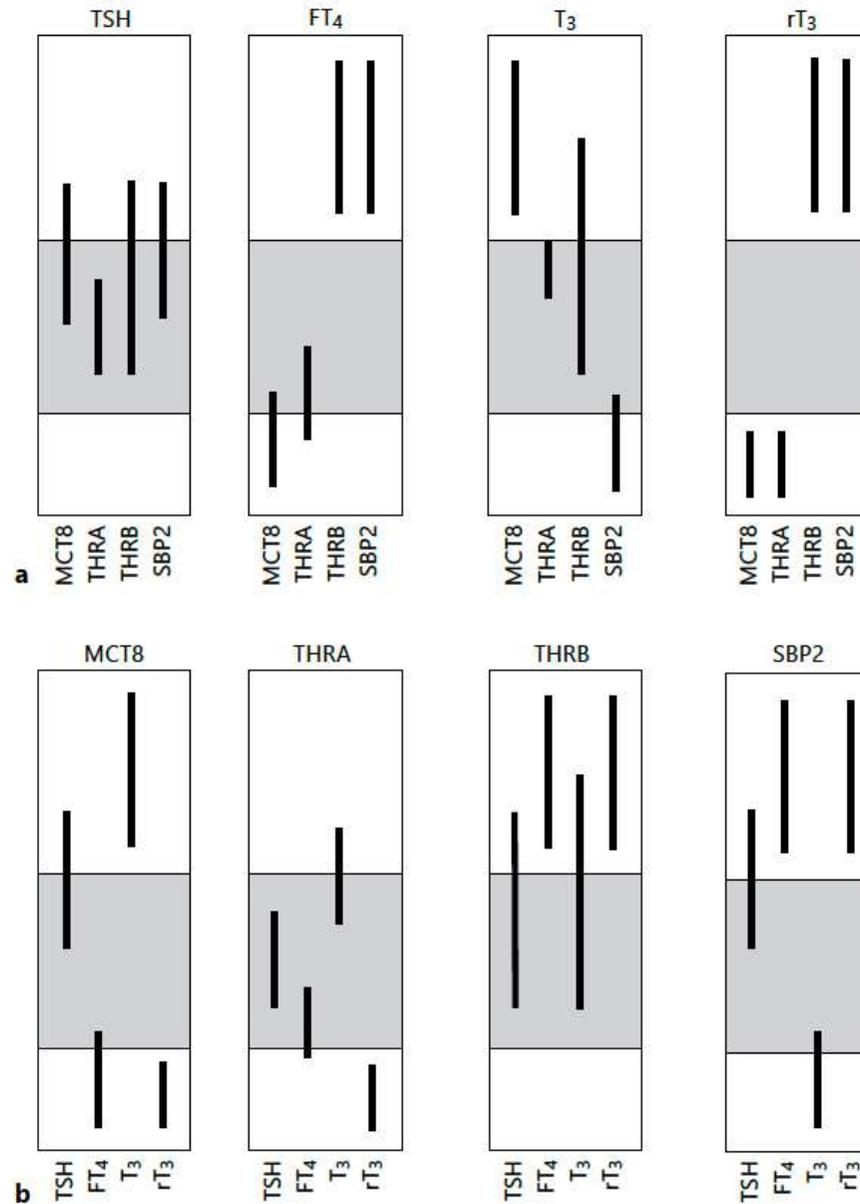
(B) Key signs



(C) Gene defect



THAD-Synopsis

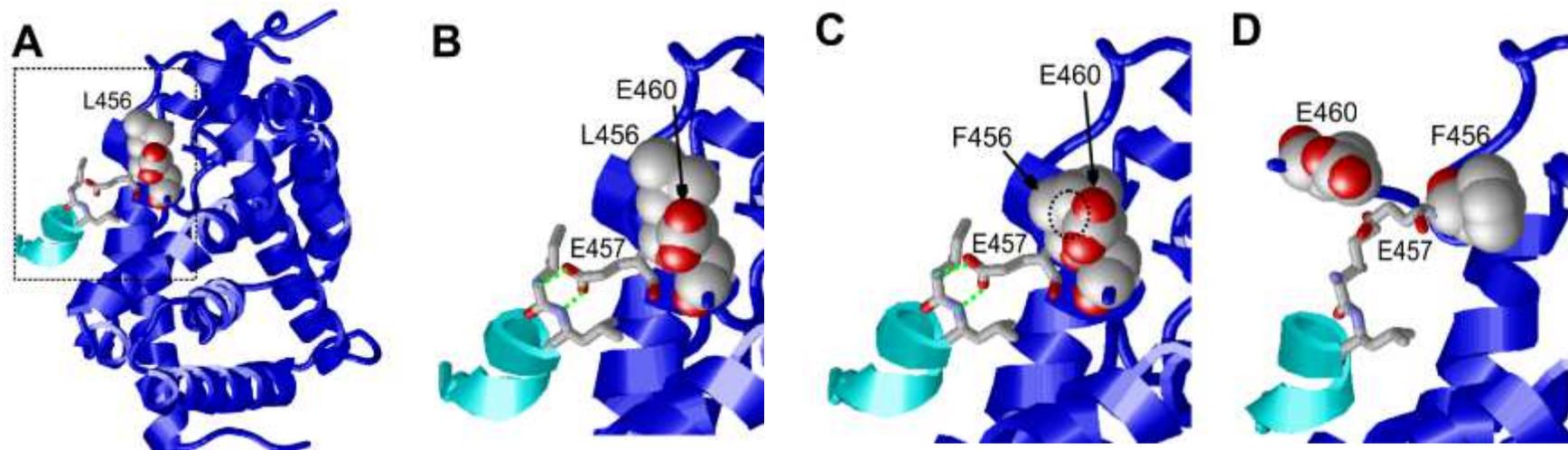


Resistance to thyroid hormone receptor beta (RTHB)

- **Inzidenz 1:40.000**
- **heterogene Klinik** (asymptomatisch bis leichte Klinik)
 - typisch Struma, Tachykardie, ADHS, ggf. verminderte Knochendichte und leichte IQ-Minderung, keine weiteren Hyperthyreose-Zeichen!
- **meist keine Therapieindikation**, ggf. symptomatisch (Betablockade)
- ggf. Behandlungsversuch mit Trijodotyhydroessigsäure → Senkung TH-Exzess
- **physiologische Integrität mglst. erhalten** (caveat Thyreoidektomie/-statika)
- **erhöhte freie SD-Hormonwerte** bei normal bis leicht erhöhtem TSH-Wert
- in 80% *THRB*-Mutation, **autosomal dominant** wg. dominant negativem Effekt
- caveat: Mütter in gebärfähigem Alter → höheres Abortrisiko (bei nicht betroffenen Feten)

In silico Analyse c.1368 L456F-Mutation

- 3 Cluster von RTHB-Mutationen → am häufigsten ligand-binding domain



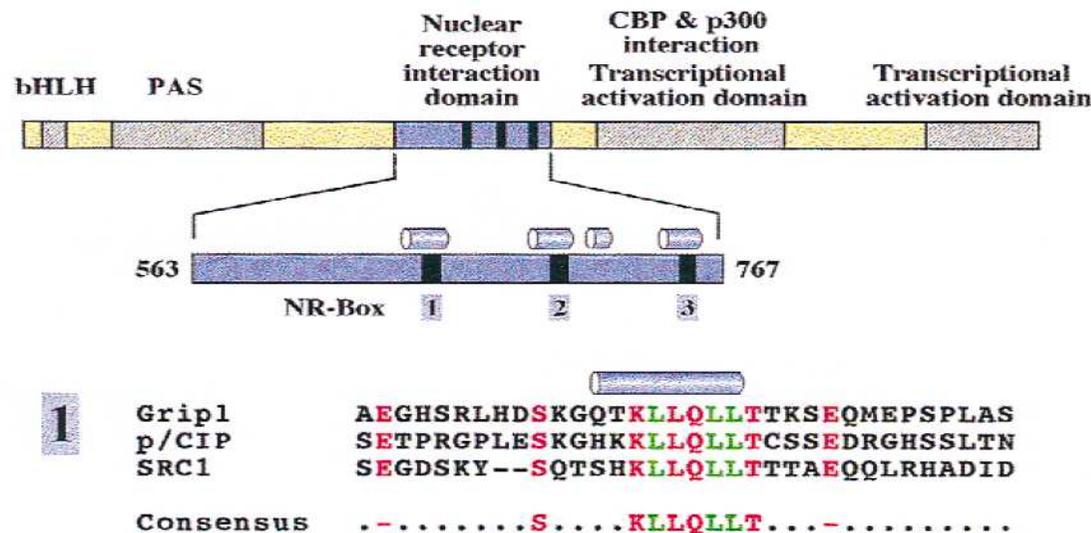
Structural effect of the L456F variant. (A) L456 is located in the ligand binding domain of THRB (cyan) in the vicinity of the GRIP1 (blue) binding site. Key residues are shown as stick or in space-filled presentation. The dashed rectangle is shown as enlargement in panel B. (B) L456 interacts with E460 (both in space-filled presentation) and polar interactions (green dotted lines) are formed between E457 and GRIP1 (both in stick presentation). (C) The L456F exchange causes steric clashes with E460 (black circle). (D) Conformational rearrangement of residues 456-460 results in a loss of the interactions with the GRIP1 coactivator

In silico Analyse c.1368 → LxxLL-Motif-Mutation

Structure and specificity of nuclear receptor-coactivator interactions

Beatrice D. Darimont,^{1,2} Richard L. Wagner,^{2,3} James W. Apriletti,⁴ Michael R. Stallcup,⁵ Peter J. Kushner,⁴ John D. Baxter,⁴ Robert J. Fletterick,⁶ and Keith R. Yamamoto^{1,7}

¹Department of Cellular and Molecular Pharmacology, ³Graduate Group in Biophysics, ⁶Department of Biochemistry and Biophysics, ⁴Metabolic Research Unit, University of California at San Francisco (UCSF), San Francisco, California 94143 USA; ⁵Department of Pathology, University of Southern California, Los Angeles, California 90033 USA



L454-Mutation als Ursache für RTH via SRC1

Proc. Natl. Acad. Sci. USA
Vol. 94, pp. 248–253, January 1997
Medical Sciences

A natural transactivation mutation in the thyroid hormone β receptor: Impaired interaction with putative transcriptional mediators

(resistance to thyroid hormone/hormone-dependent transactivation/coactivator)

T. N. COLLINGWOOD*[†], O. RAJANAYAGAM*[†], M. ADAMS*, R. WAGNER[‡], V. CAVAILLÈS[§], E. KALKHOVEN[§],
C. MATTHEWS*, E. NYSTROM[¶], K. STENLOF[¶], G. LINDSTEDT[¶], L. TISELL[¶], R. J. FLETTERICK[‡], M. G. PARKER[§],
AND V. K. K. CHATTERJEE*

*Department of Medicine, University of Cambridge, Level 5, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ, United Kingdom; [†]Department of Biochemistry and Biophysics, University of California, San Francisco, CA 94143-0448; [¶]Sahlgren's University Hospital, University of Gothenburg, S-41345 Gothenburg, Sweden; and [§]Molecular Endocrinology Laboratory, Imperial Cancer Research Fund, Lincoln's Inn Fields, London WC2A 3PX, United Kingdom

TSH-produzierendes Mikroadenom und/oder RTH?

0021-972X/99/7604-1025\$03.00/0
Journal of Clinical Endocrinology and Metabolism
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Thyrotropin-Producing Microadenoma Associated with Pituitary Resistance to Thyroid Hormone

KENJI WATANABE, TORU KAMEYA, AKIRA YAMAUCHI, NAOHITO YAMAMOTO, AKIRA KUWAYAMA, IZUMI TAKEI, HIROSHI MARUYAMA, AND TAKAO SARUTA

Department of Internal Medicine, Keio University School of Medicine, Tokyo 160; Department of Pathology, Kitasato University School of Medicine (T.K.), Kanagawa 228; Department of Neurosurgery, Kainan Hospital (N.Y.), Aichi 498; and Department of Neurosurgery, Nagoya University School of Medicine (A.K.), Nagoya 466 Japan

ABSTRACT

A 21-yr-old female with hyperthyroidism is described. Though her serum-free T_3 was 17.8 pmol/L and free T_4 was 60.2 pmol/L, TSH was as high as 10.7 mU/L. TRH stimulated an increase in TSH from 10.7–91.7 mU/L. T_3 administration in gradually increasing doses of 100, 200, and 400 mg/day resulted in gradual reduction in serum TSH. Cranial computed tomography and magnetic resonance imaging revealed a microadenoma of the pituitary gland. Histology of the surgical specimen showed a TSH-producing adenoma with TSH cell cluster

islets and decreased numbers of TSH cells in the nonneoplastic pituitary. Cultured cells from the adenoma secreted TSH spontaneously and in response to TRH. This TRH-stimulated TSH secretion was suppressed by T_3 in a dose-dependent manner. One year postoperatively, neither residual tumor nor recurrence were seen by computed tomography and magnetic resonance imaging. However TSH, as well as free T_3 or T_4 , was still high and overresponsive to TRH. (*J Clin Endocrinol Metab* 76: 1025–1030, 1993)

A Patient With a Thyrotropin-Secreting Microadenoma and Resistance to Thyroid Hormone (P453T)

J Clin Endocrinol Metab, July 2015, 100(7):2511–2514

Xiaochun Teng, Ting Jin, Gregory A. Brent, Anhua Wu, Weiping Teng, and Zhongyan Shan

Department of Endocrinology and Metabolism (X.T., T.J., W.T., Z.S.), Institute of Endocrinology, Liaoning Provincial Key Laboratory of Endocrine Diseases, The First Affiliated Hospital of China Medical University,

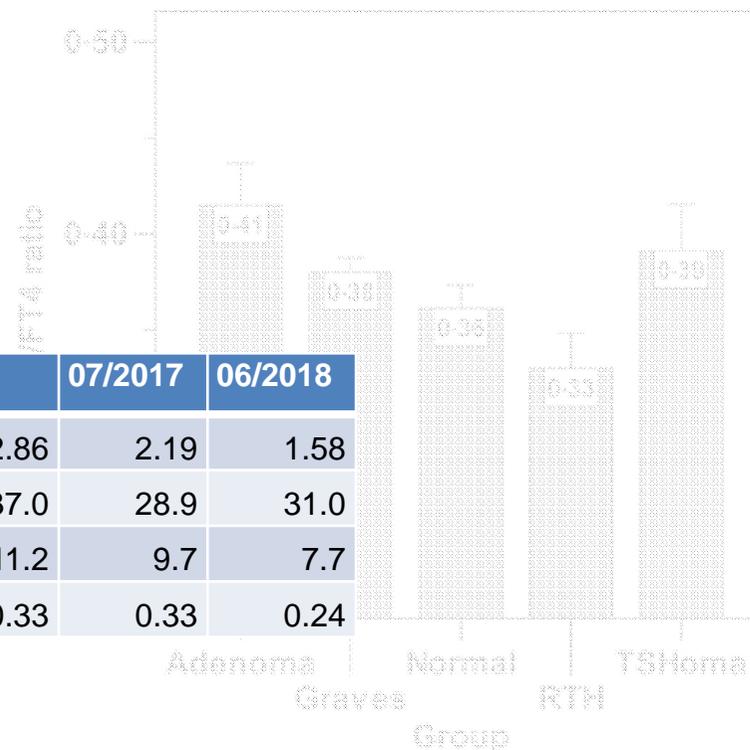
TSHoma vs. RTH

- TSHoma häufiger Makroadenome (82-88 % vs. 13-18 %)
- Wachstumstendenz

TSHoma vs. RTH

■ fT3/fT4-Ratio

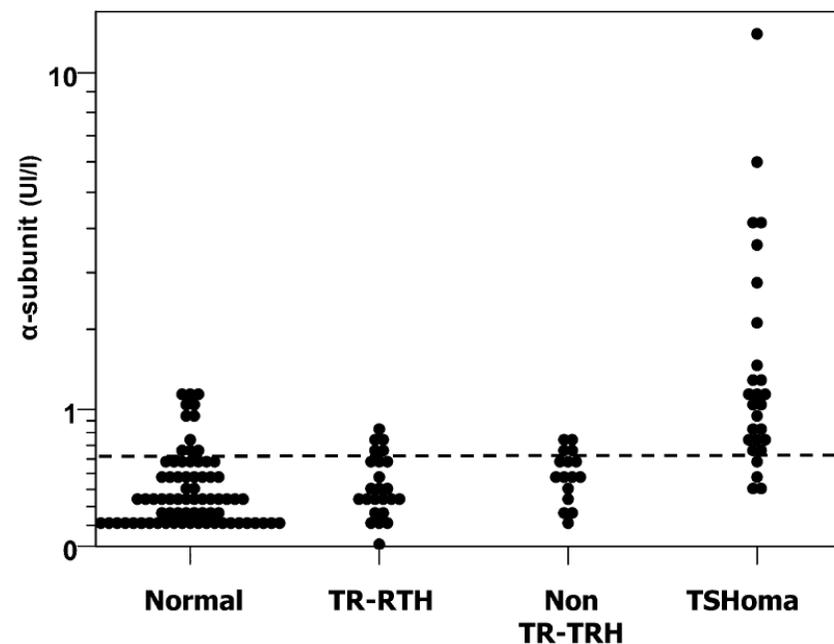
	unit	12/2016	02/2017	04/2017	07/2017	06/2018
TSH	mIU/l	1.93	1.99	2.86	2.19	1.58
fT4	pmol/l	25.7	29.1	37.0	28.9	31.0
fT3	pmol/l	8.6	8.2	11.2	9.7	7.7
fT3/fT4 ratio		0.33	0.28	0.33	0.33	0.24



Parameter (normal values)	All RTH (IQR*)	TR-RTH (IQR)	Non-TR-RTH (IQR)	TSHoma (IQR)	P-value (TR-RTH vs non-TR-RTH)	P-value (all RTH vs TSHoma)	P-value (non-TR-RT vs TSHoma)
Age	28 (17–48)	28 (13–39)	41 (28–60)	47 (37–56)	0.026	< 0.001	0.406
TSH (μUI/ml) (0.4–3.4)	1.7 (1.2–2.4)	1.7 (1.2–2.6)	1.7 (1.1–2.2)	3.2 (2.1–3.8)	0.928	< 0.001	0.002
FT3 (pg/ml) (2.7–5.7)	7.0 (5.9–8.5)	7.0 (6.3–8.7)	6.8 (5.9–8.5)	7.9 (6.5–10.8)	0.651	0.013	0.035
FT4 (pg/ml) (7–17)	25.3 (22–29.5)	25.6 (21.7–29.7)	24.9 (23.4–29.0)	24.6 (21.7–32.9)	0.974	0.966	0.892
FT3/FT4 ratio (0.28–0.42)	0.32 (0.28–0.37)	0.33 (0.28–0.37)	0.29 (0.26–0.34)	0.39 (0.34–0.45)	0.337	< 0.001	0.002

TSHoma vs. RTH

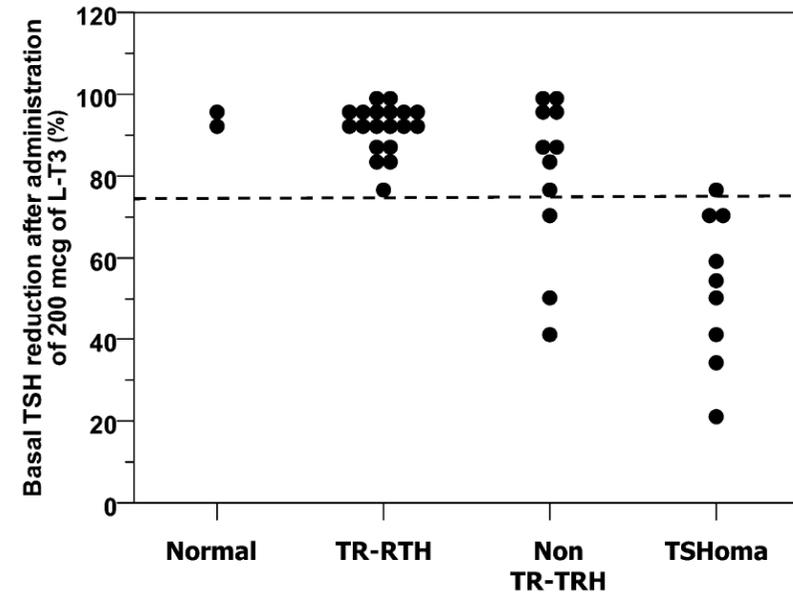
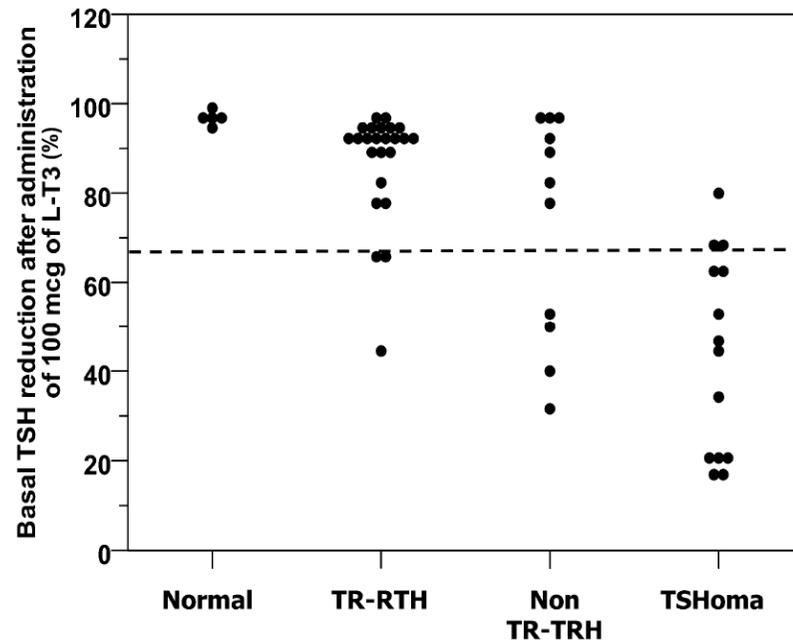
- alfa-Subunit 06/2018: 0.61 (< 1.3 U/l)
- alfa-Subunit/TSH molar ratio 06/2018: 0.38
- SHBG 06/2018: 72 nmol/l (27.1-128 nmol/l)



Parameter (normal values)	All RTH (IQR*)	TR-RTH (IQR)	Non-TR-RTH (IQR)	TSHoma (IQR)	<i>P</i> -value (TR-RTH vs non-TR-RTH)	<i>P</i> -value (all RTH vs TSHoma)	<i>P</i> -value (non-TR-RT vs TSHoma)
A-SU (mUI/l) (<0.9;<1.6)	0.4 (0.2–0.5)	0.3 (0.2–0.5)	0.41 (0.3–0.6)	1.0 (0.6–2.1)	0.148	<0.001	<0.001
Molar ratio (<2.4)	2.0 (1.1–2.7)	1.33 (0.77–0.78)	2.44 (1.56–3.24)	4.1 (2.6–7.1)	0.078	<0.001	0.022
SHBG (nmol/l) (27–92)	28.0 (18.3–51.7)	28.0 (19.3–48.8)	41.5 (17.8–60.9)	73.2 (51.1–88.0)	0.616	<0.001	0.011

TSHoma vs. RTH

- T3-Suppressions-Test über 3 Tage



TSHoma vs. RTH-Synopsis

	Relevanz	TSHoma	RTH
Grösse		eher Makroadenom	eher Mikroadenom(e)
Wachstumstendenz		ja	mglw.
TSH-level		eher erhöht	normal bis leicht erhöht
alfa-SU	3	hoch	normal
alfa-SU/TSH ratio	2	erhöht	niedrig
SHBG		hoch	normal
fT3/fT4 ratio		erhöht	normal
TSH-Fest unter T3-Substitution	4	gut stimulierbar	kaum Ansprechen
T3-Suppressionstest	1	supprimierbar	kaum Ansprechen
Somatostatin-Behandlung		SD-Hormon-Normalisierung	kein Ansprechen

Take home

- RTH seltene Erkrankung und wichtigste DD für TSHoma
 - am häufigsten Mutationen in *THRB*
- RTHB gekennzeichnet durch Struma, Tachykardie, ADHS
- Kalorimetrie hilfreich für Abgrenzung unklarer SD-Hormonerhöhung
- Diagnose erzwingen → Genetische Analyse bei Verdacht auf RTH anstreben
- thyreostatische Behandlung resp. Thyreoidektomie mglst. vermeiden

Pocketguide



20. Hyperthyreose & TSH-Suppression



"Hormone" (greek): impelling, exciting, setting in motion...

Lancet 03; 362: 459-68, JCEM 03: 88: 3474-81 & 05; 90: 5234-40, NEJM 16; 375:1552-65; SMF 05; 5: 933-5, www.basedow.ch

Hyperthyreose Prävalenz 2.5%, F>M

DD: Basedow (BAS; junge F, EOP (60%), TRAK) > **Autonomie** (TXA/MFA ("tox. Knotenstr.") >45j, palp. Knoten, Jodmangel)

> **Thyreoiditis** RAJ uptake↓: **DQV** (Sz, BSR↑), **Silent** (RF: Infeon-Th, postpartal, kein Sz, transient T4↑, oft TPO-Ak pos⇒Hypothyreoserisiko↑)

Th: **Sz**: NSAID u/o Prednison 0.5mg/kg, **Sy**: β-Blocker, kein CBZ/PTU); **Amiodarone** (su), > **HCG** (hyperemesis grav) / **SS** (max 12 SSW) > **Factitia**
(Tg↓, sekundär (TSH α-subunit↑), Hypophysäre T4-Resistenz Str. Ovarii;

SY: zT atypisch („Altersdemenz“, hypokaliäm. thyrotox. period. Paralyse "HTPP"), Quantifizierung & Verlaufsko→ **Zulewski II Score**:

Typisch: Nervosität; Schwitzen↑ (**DD**); Palpitationen; Stuhlfrequenz↑; Gew↓ (trotz Appetit↑); Schlafstörungen

Hyperkinetische Bewegungen; warme/feuchte Haut; Puls>90, Fingertremor; Struma ≥ I („tastbare SD“), EOP (su),

DG: TSH↓, nur **fT4↑** (Jodexpos, Amiodaron, NTI, Steroide, B-Blocker), nur **T3↑**(Frühphase); b Pille/SS→fT3 bestimmen