CENTRAL HYPOTHYROIDISM

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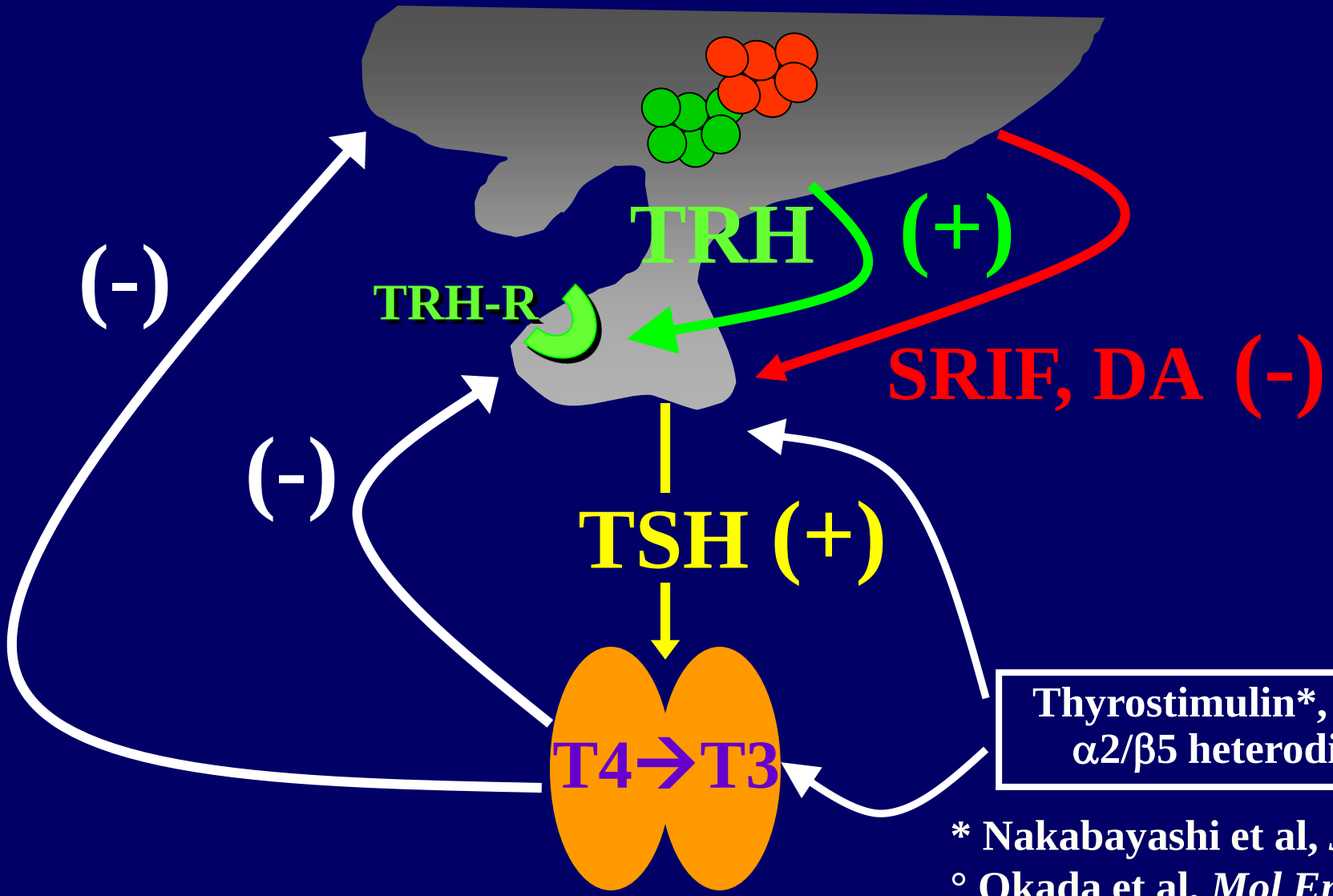
Definition and epidemiology

Central hypothyroidism is defined as reduced thyroid hormone secretion resulting from deficient stimulation of an intrinsecally normal thyroid gland by TSH.

Prevalence: 1:20,000 - 1:80,000

Hypothalamic-pituitary-thyroid axis



* Nakabayashi et al, *JCI* 2002

° Okada et al, *Mol Endo* 2006

TABLE 2. Effect of transsphenoidal surgery in clinically nonfunctioning adenomas on pituitary function

	Arafah *et al.* (32)	Comtois *et al.* (33)	Marazuela *et al.* (30)	Greenman *et al.* (29)	Wichers-Rother *et al.* (27)	Nomikos *et al.* (34)	Alameda *et al.* (28)	Dekkers *et al.* (22)
No. of patients	26	126	35	26	109	660	51	109
Time after surgery for evaluation of pituitary function (months)	0.2	ND	2–6	3–6	1–6	12	ND	6
Clinical symptoms								
Visual field defects (%)	73	78	60	ND	63	31	62	87
Tumor characteristics								
Suprasellar extension (%)	80	94	80	96	ND	ND	82	96
Parasellar/infrasellar extension (%)	ND	33	84	42	ND	ND	48	36
Pituitary: preoperative function								
GH deficiency (%)	100	ND	88	ND	85	ND	80	77
LH/FSH deficiency (%)	96	75	69	78	61	77	62	75
TSH deficiency (%)	81	18	23	23	31	19	21	43
ACTH deficiency (%)	62	36	29	43	32	35	19	53
Hypopituitarism (%)	ND	73	69	89	ND	85	85	83
Pituitary: postoperative function								
GH deficiency (%)	85	ND	82	ND	78	ND	88	83
LH/FSH deficiency (%)	65	70	48	46	50	65	57	90
TSH deficiency (%)	35	31	20	12	34	16	27	57
ACTH deficiency (%)	38	29	13	50	25	18	19	60
Hypopituitarism (%)	ND	ND	ND	65	ND	72	89	94

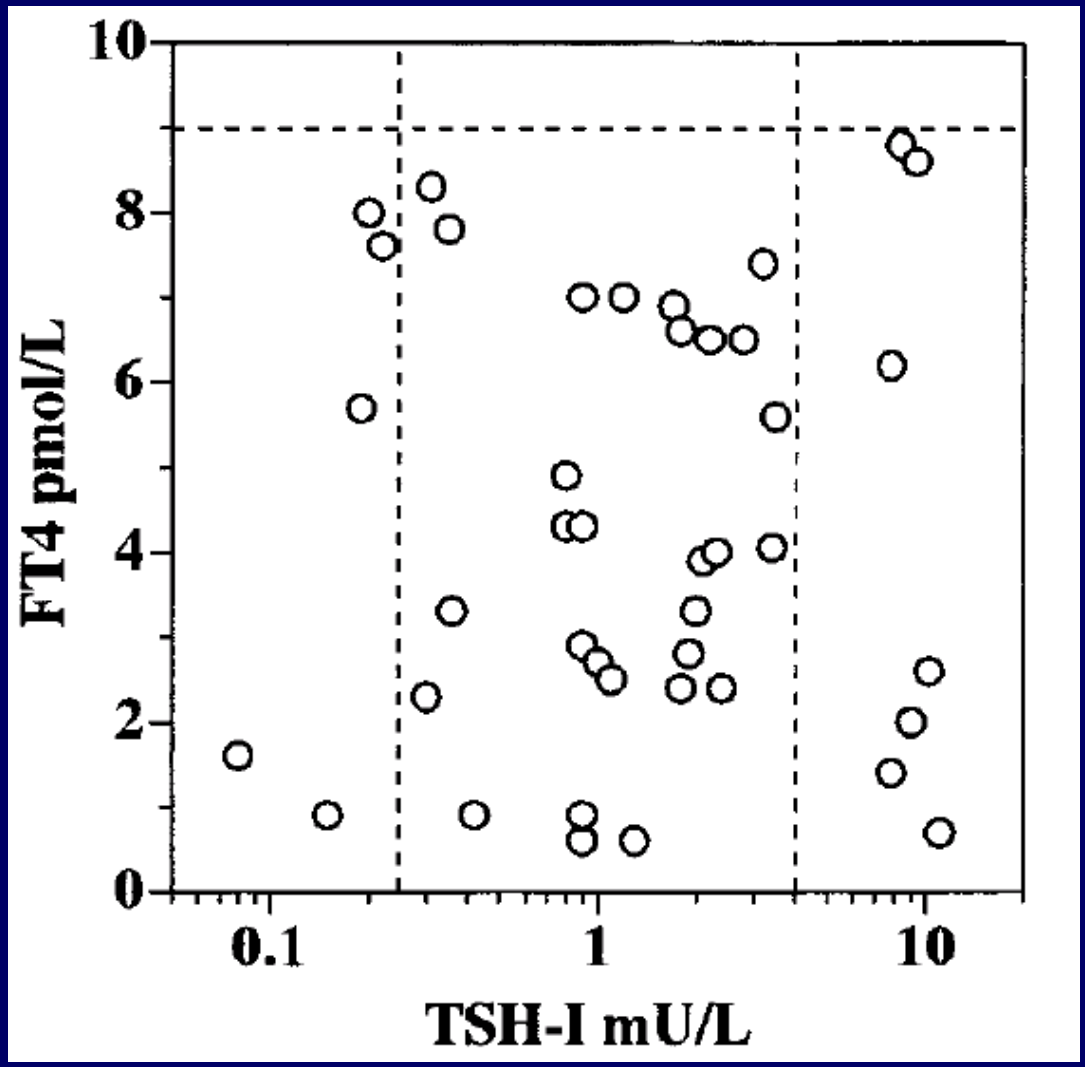
ND, Not documented.

Dekkers OM, Pereira AM, Romijn JA. Treatment and follow-up of clinically nonfunctioning pituitary macroadenomas. JCEM 2008;93:3717

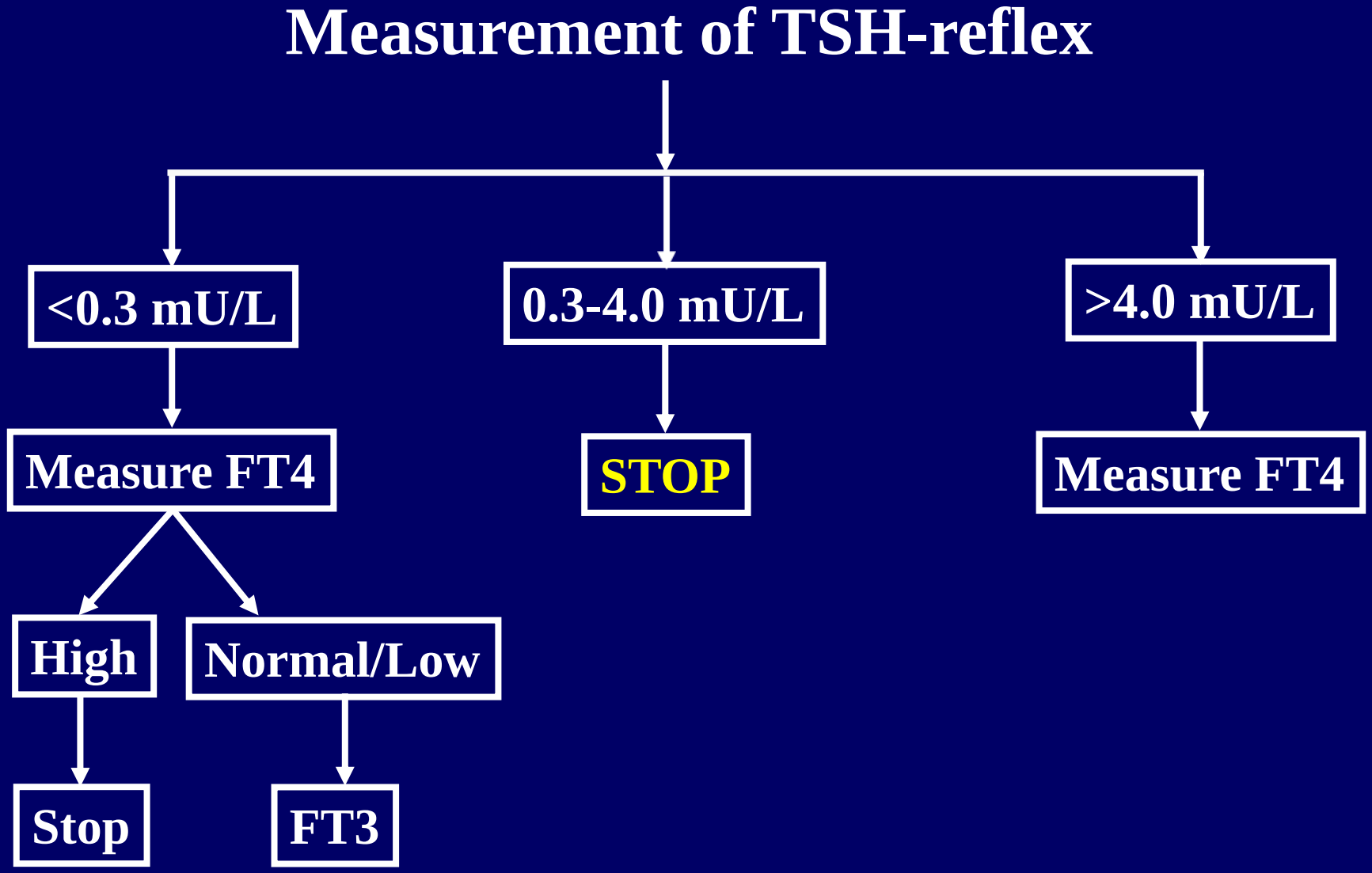
Question #1

How can you diagnose central hyopothyroidism?

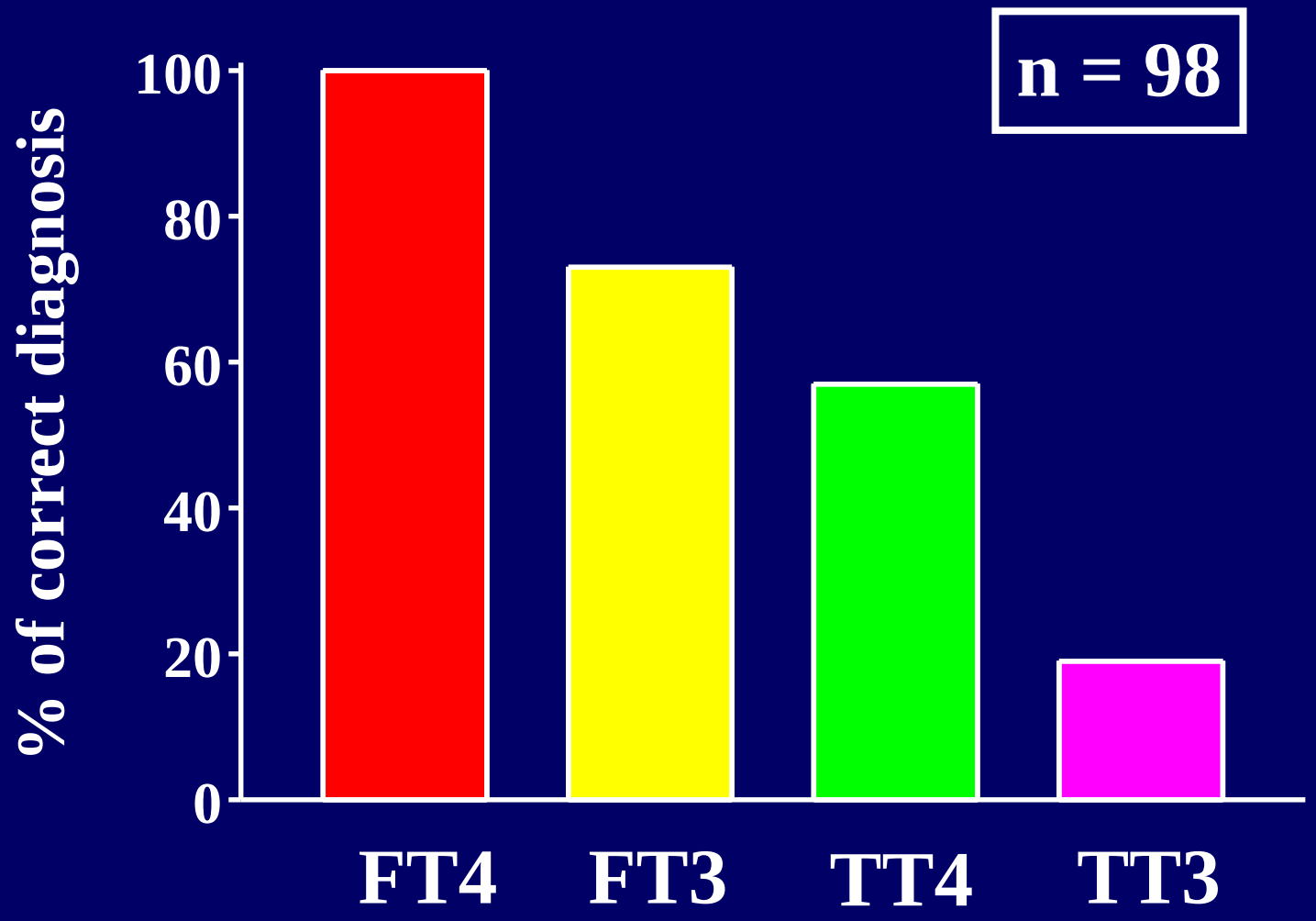
Serum TSH and free T4 in central hypothyroidism



The problem of TSH-reflex in central hypothyroidism



Diagnostic accuracy of various thyroid function parameters.



Decrease of circulating T4 levels more than 20% of the initial T4 determination may indicate central hypothyroidism in patients with different pituitary disorders, even if FT4 values are still into the normal range

Alexopoulou et al., Eur J Endocrinol 2004; 150: 1-8

CLINICAL PICTURE

- **Signs and symptoms of hypothyroidism**

(weakness, sensation of cold, dry skin, decreased sweating, lethargy, slow speech, impaired memory, constipation, gain in weight, anorexia, nervousness, anemia)

- **Manifestations of concomitant or pre-existing hypothalamic/pituitary disease**

- **Altered MRI of hypothalamic-pituitary**

•region

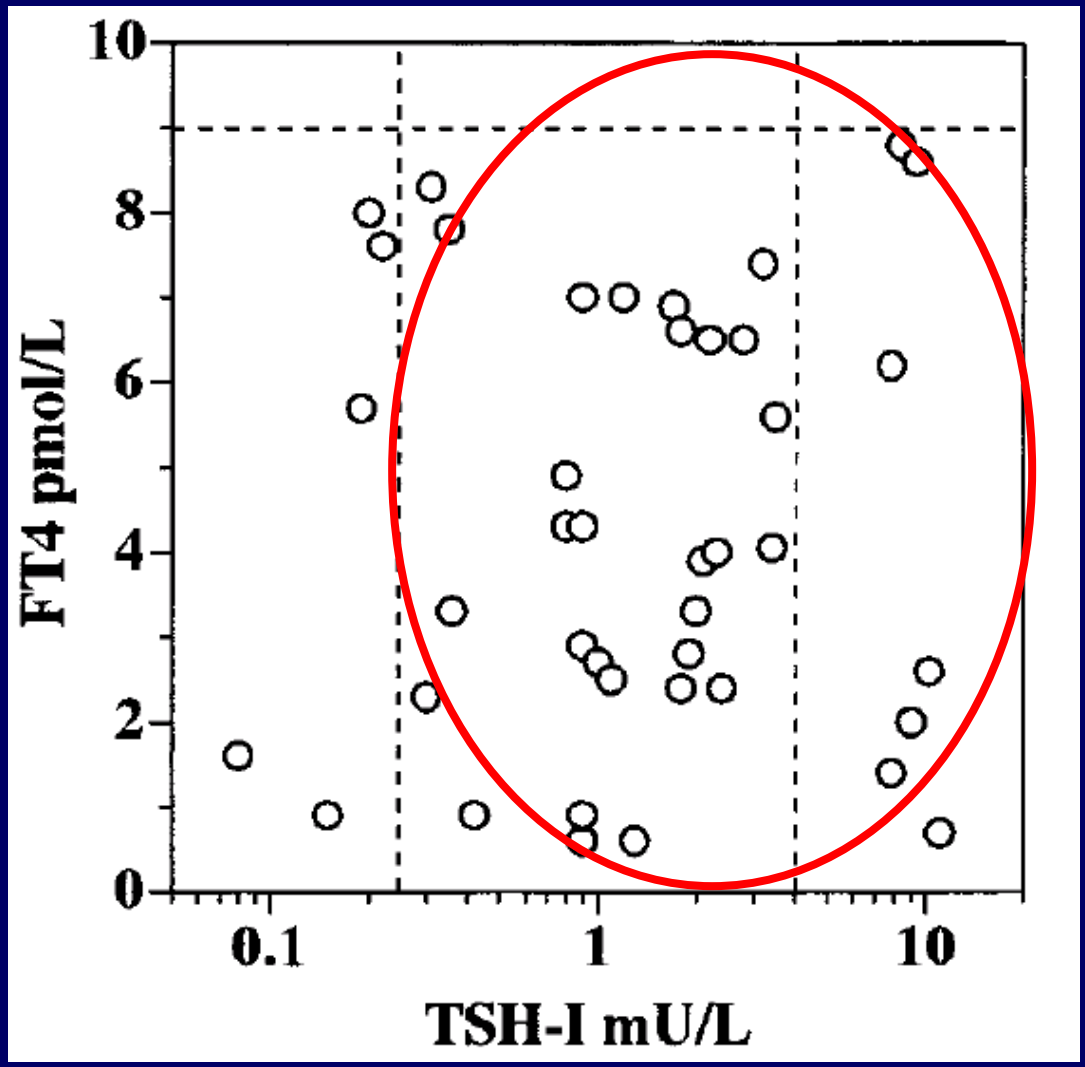
Question #2

Any additional characteristics of patients with central hypothyroidism?

Additional characteristics of patients with central hypothyroidism

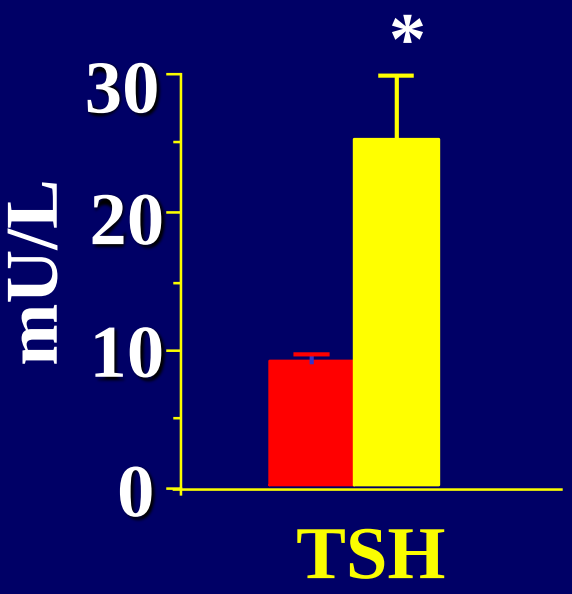
- Absence of Tg-Ab and TPO-Ab
- Reduced Thyroidal Uptake (RAIU)
- Normal thyroid response to exogenous rhTSH both in term of thyroid hormone secretion and RAIU

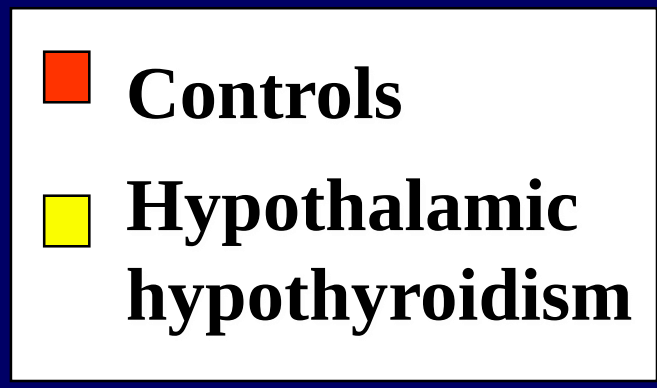
Serum TSH and free T4 in central hypothyroidism

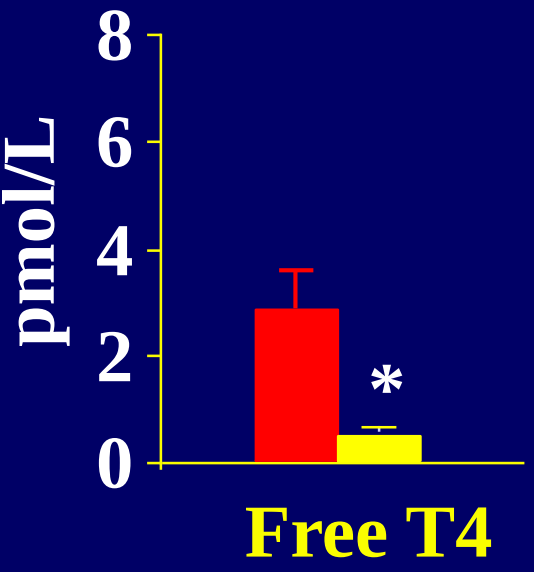


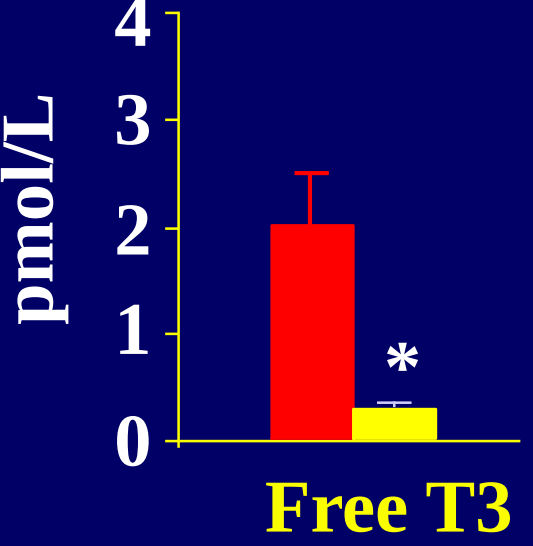
Net increments after TRH injection

* *P*<0.01 *vs* controls









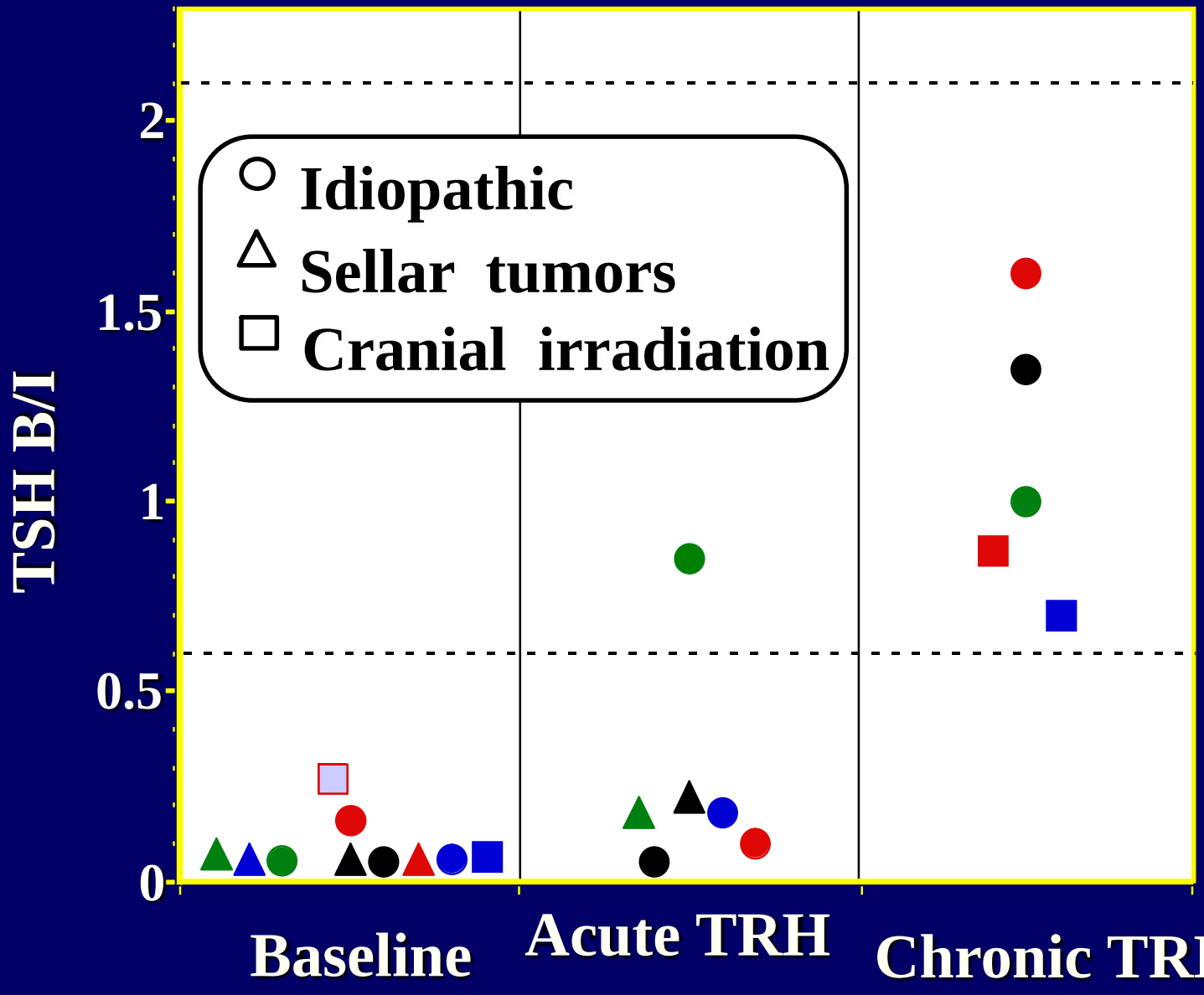
Beck-Peccoz&Persani, European Journal of Endocrinology 1994; 131: 331

Question #3

What is the reason for normal/elevated serum TSH levels?

CENTRAL HYPOTHYROIDISM

TSH bioassay in CHO-R cells



Causes of hypopituitarism: the 9 "I" + 1 "M"

- INVASIVE
- INFARCTION (postpartum necrosis, apoplexy)
- INFILTRATIVE (hemochromatosis, sarcoidosis)
- INJURY (head trauma)
- IMMUNOLOGIC (lymphocytic hypophysitis)
- IATROGENIC (post-surgery, post-radiations)
- INFECTIOUS (tubercolosis)
- IDIOPATHIC
- ISOLATED

+ 1 M: Malformations (primary empty sella)

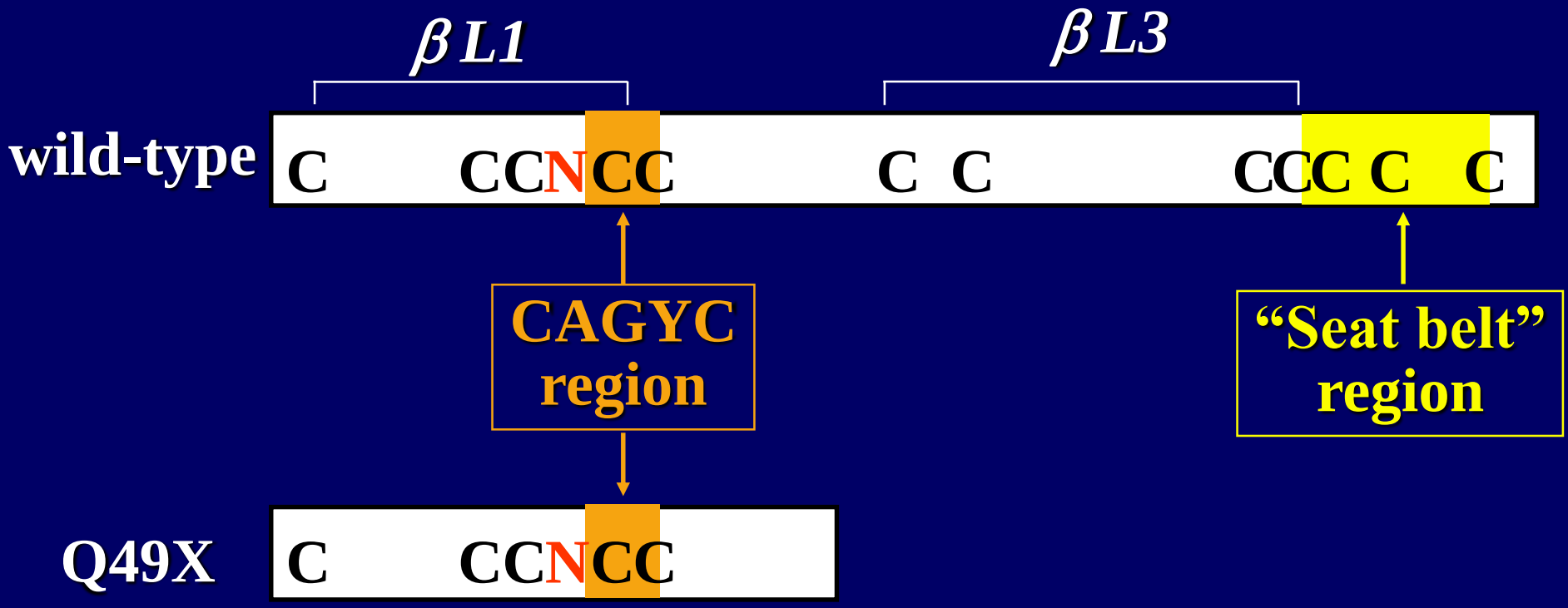
Genetic forms of central hypothyroidism

Gene (Locus)	Endocrine phenotype	Associated features	Inheritance	Biochemical tests
TSHβ	Severe isolated CH with neonatal onset		Recessive	TSH: low/normal α-GSU: high
TRH-R	Isolated CH with neonatal onset		Recessive	TSH: low/normal TRH test: blunted TSH and PRL response
PIT1 (POU1F1)	Moderate/severe CH with combined GH and PRL defects and neonatal/ infantile onset		Dominant or recessive	TSH: low/normal
PROP1	Moderate/severe CH with combined GH, PRL, LH/FSH, ACTH defects and neonatal/infantile onset		Recessive	TSH: low/normal
HESX1	Severe CH with GH, PRL, LH/FSH, ACTH combined defects	Septo-optical dysplasia (SOD)	Dominant or recessive	TSH: undetectable
LHX3	Severe CH with GH, PRL, LH/FSH combined defects	Rigid cervical spine	Recessive	TSH: low/normal

Family 3

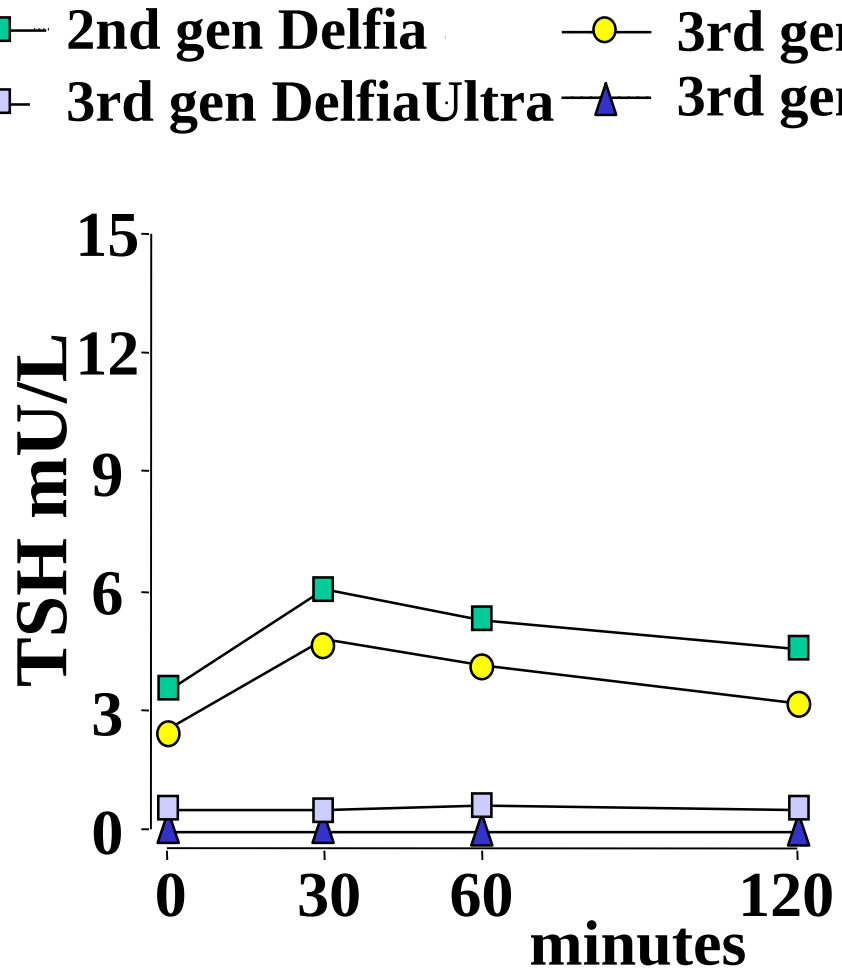
- 8-yr-old baby, consanguineous parents, low birth weight,
- “normal” at CH neonatal screening based on TSH measurement,
- at the age of 75 days many clinical signs of hypothyroidism,
- TSH=3.7 mU/L, FT4=2.6 pmol/L,
- normal secretion of other pituitary hormones,
- no thyroidal uptake, hypoplastic thyroid at the ecography,
- hyperplastic pituitary at the MRI,
- Start L-T4 at the age of 81 days ----> cretinism

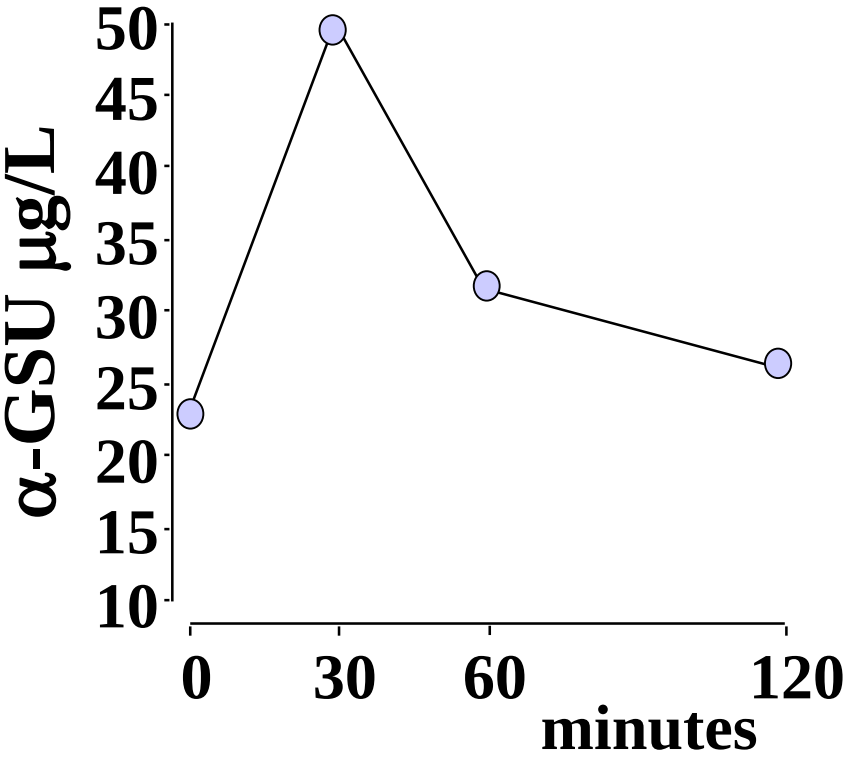
TSHβ subunit



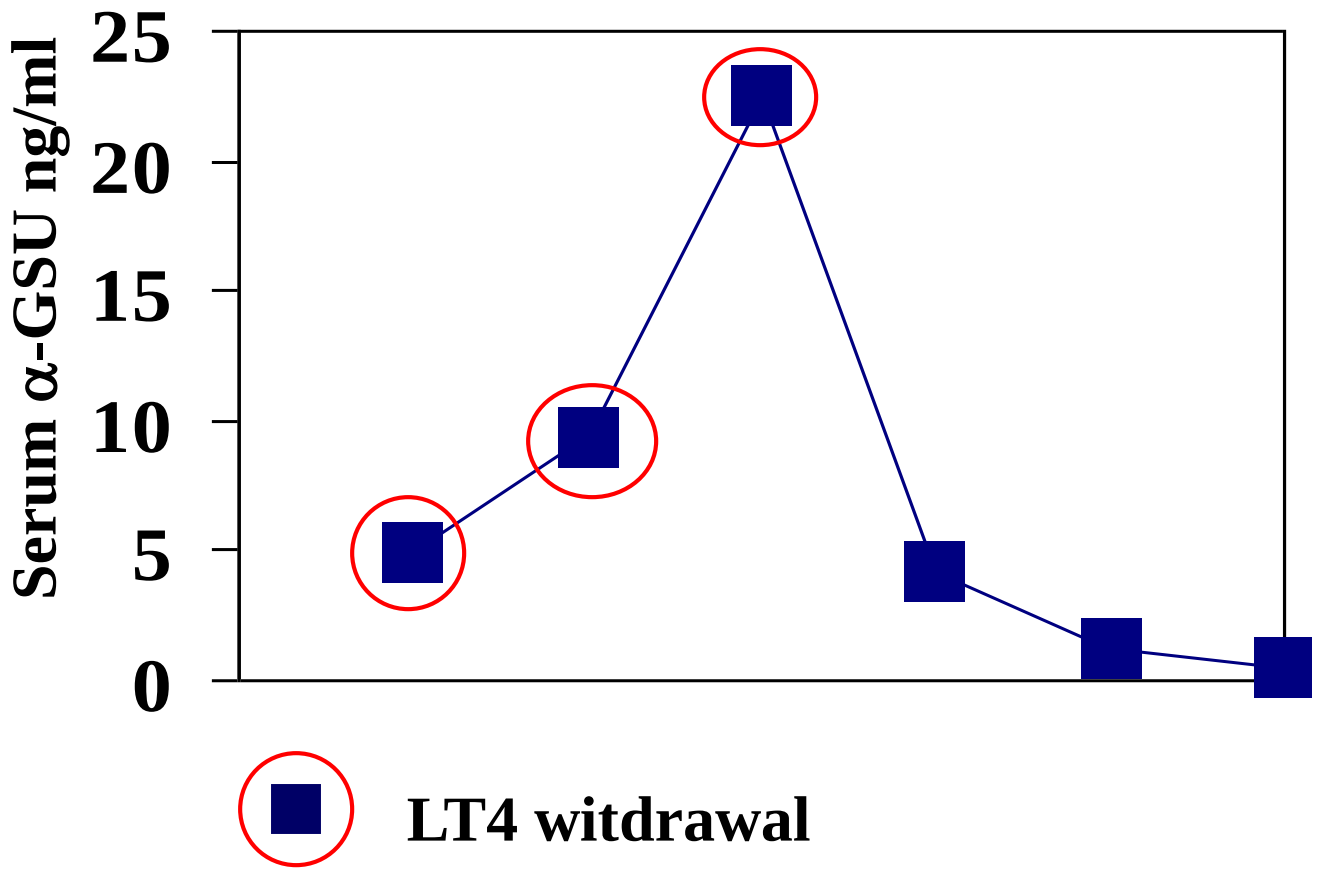
C, cysteine
N (Asn23), site of N-glycosylation

TRH test (7.0 µg/kg i.v.)



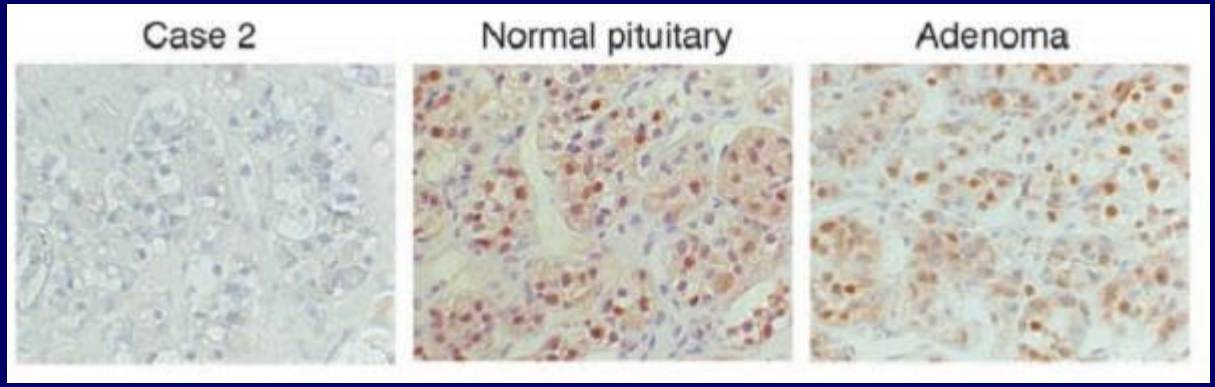


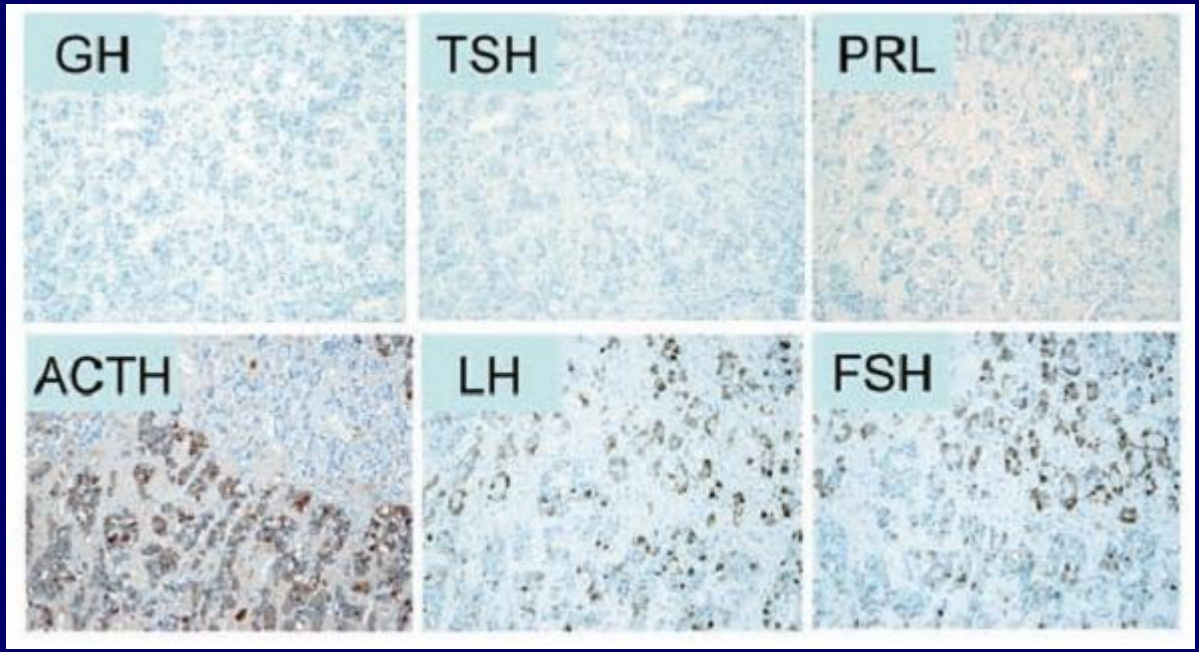
Monotoring serum levels of α-GSU in one patient with TSHβ gene mutation



Adult combined GH, prolactin, and TSH deficiency associated with circulating PIT-1 antibody in humans

Yamamoto et al., J Clin Invest. 121: 113-119; 2011


Case 2
Normal pituitary
Adenoma


GH
TSH
PRL
ACTH
LH
FSH

Loss-of-function mutations in *IGSF1* cause a novel X-linked syndrome of TSH deficiency and macroorchidism

Yu Sun[1,19], Beata Bak[2,19], Nadia Schoenmakers[3,19], A.S. Paul van Trotsenburg[4,19], Peter Voshol[3], Emma Cambridge[5], Jacqui White[5], Paul le Tissier[6], S. Neda Mousavy Gharavy[7], Juan P. Martinez-Barbera[7], Wilma Oostdijk[8], Wilhelmina J Stokvis-Brantsma[8], Thomas Vulsma[4], Marlies J Kempers[4,9], Luca Persani[10], Irene Campi[11], Marco Bonomi[10], Paolo Beck-Peccoz[11], Hongdong Zhu[12], Timothy Davis[12], Jose C Moreno[13], Anita C.S.Hokken-Koelega[14], Dasha Gorbenko[14], Adela Escudero[13], Jayanti Rangasami[15] , Claudia A.L. Ruivenkamp[1], Jeroen Laros[1], Marjolein Kriek[1], Sarina G. Kant[1], Cathy Bosch[1],Nienke R. Biermasz[16], Natasja M. Appelman-Dijkstra[16], Alberto M.Pereira[16], Johan den Dunnen[1,17], Martijn H. Breuning[1], Raoul C.Hennekam[4], Krishna Chatterjee[3], Mehul T. Dattani[18,20], Jan M. Wit[8,20], Daniel J. Bernard[2,20]

IGSF1 **encodes an integral membrane glycoprotein highly expressed in anterior pituitary gland. Disease-associated** ***IGSF1*** **mutations impaired plasma membrane trafficking of the IGSF1 protein.** ***Igsf1*** **deletion in male mice caused significant decreases in intra-pituitary TSH and circulating thyroxine. Collectively, these data suggest that loss of function mutations in X-linked** ***IGSF1*** **cause lifelong TSH deficiency, adult macroorchidism, and variable prolactin deficiency.**

Question #4

Which is the treatment of central hypothyroidism?

Treatment of central hypothyroidism rests on morning administation of L-Thyroxine.

Treatment of central hypothyroidism

Start treatment with low doses of L-T4 (25 µg/day or less taking into consideration patient body weight) and increase the dose every 3-6 weeks pondering the severity and the duration of the disease. Remind to take the pills at least half an hour before breakfast.

Rule out the possible presence of central hypoadrenalism.

Start cortisol or cortisone treatment BEFORE that of LT4 therapy.

Monitoring LT4 substitutive therapy

- **Withdraw blood *before* LT4 administration.**
- **Maintain serum FT4 levels between 13-15 pmol/L, if the normal range is 9-20 pmol/L.**
- **If doubts, measure some parameters evaluating peripheral thyroid hormone action (see *Ferretti et al, JCEM 1999*).**

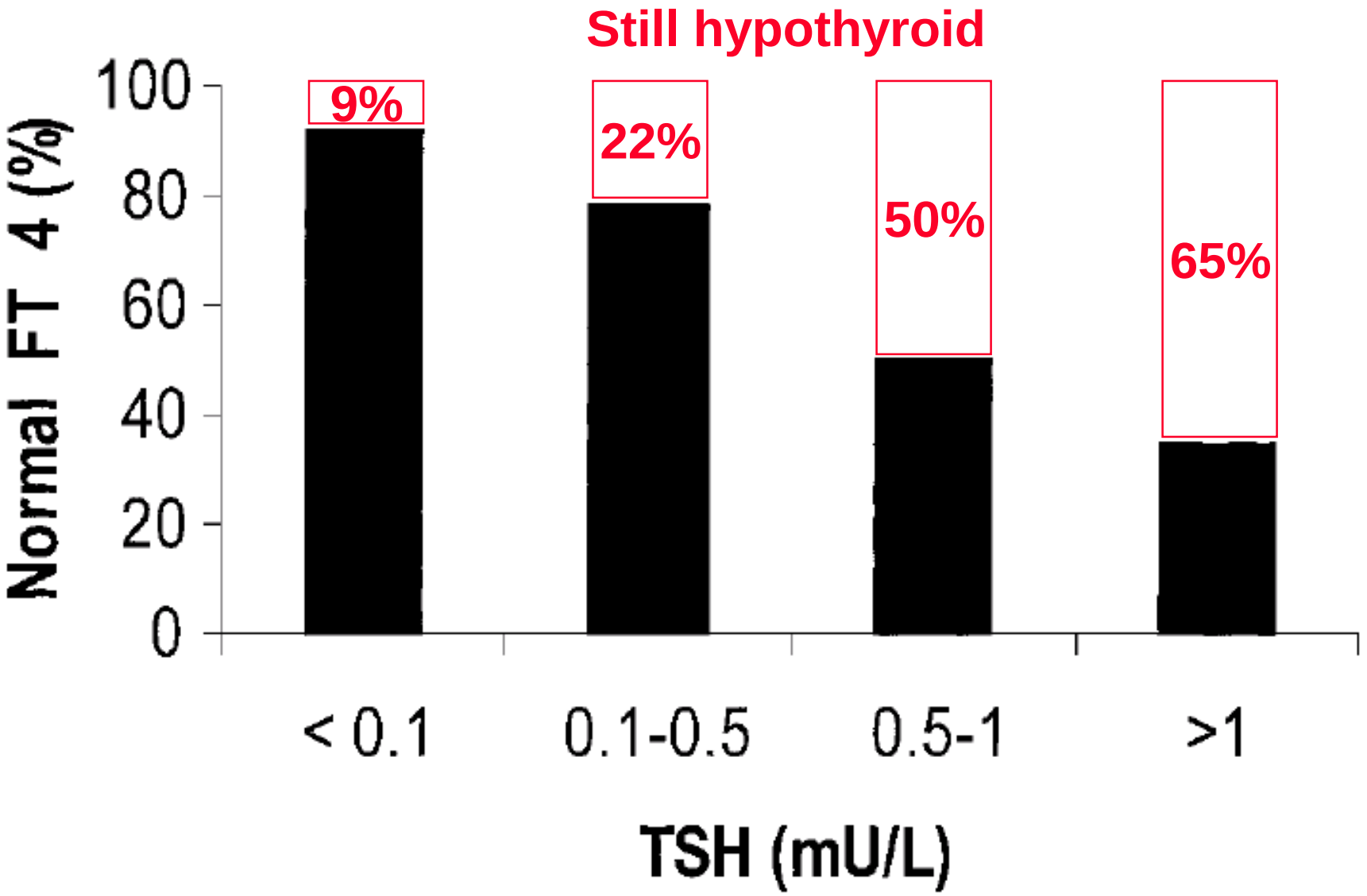
Tailor the dose for each individual patient!!

Table 3. Distributions of free T4 values in patients with pituitary disease and controls with primary thyroid disease

	Number	fT4 10th centile	fT4 median	fT4 90th centile	Below Ref. range	Above Ref. range	fT4 ≤ 11	fT4 ≤ 13
High risk pituitary –on T4	131	10	15	20	3·8%	0·8%	20·6%	38·9%†
TSC controls – on T4	1357	14	17	21	0%	0·8%	1·5%	9·5%†

Koulouri et al., Clin Endocrinol (Oxf) 2011: 74, 744

Retrospective study of CH patients on LT4 therapy



Shimon et al, Thyroid 2002

In conclusion, L-T4 substitutive therapy might be optimal if the following conditions are fulfilled:

a) start therapy only after exclusion of adrenal insufficiency,
b) establish the final dose based on age and sex (1.4-1.7 μg/kg bw),
c) maintain the levels of circulating FT4 in the middle of the laboratory reference values,
d) reassess the dose of L-T4 whenever additional replacement with other pituitary hormones is necessary,
e) be sure during the follow-up that blood for FT4 measurement is withdrawn before ingestion of daily L-T4 tablets,
f) suspect undertreatment when TSH levels are >0.2 mU/L,
g) in iodine-deficient countries, consider the possible presence of a nodular goiter with autonomous thyroid hormone secretion in order to prevent possible L-T4 overtreatment.