
ENDOCRINE PMK

Case 4

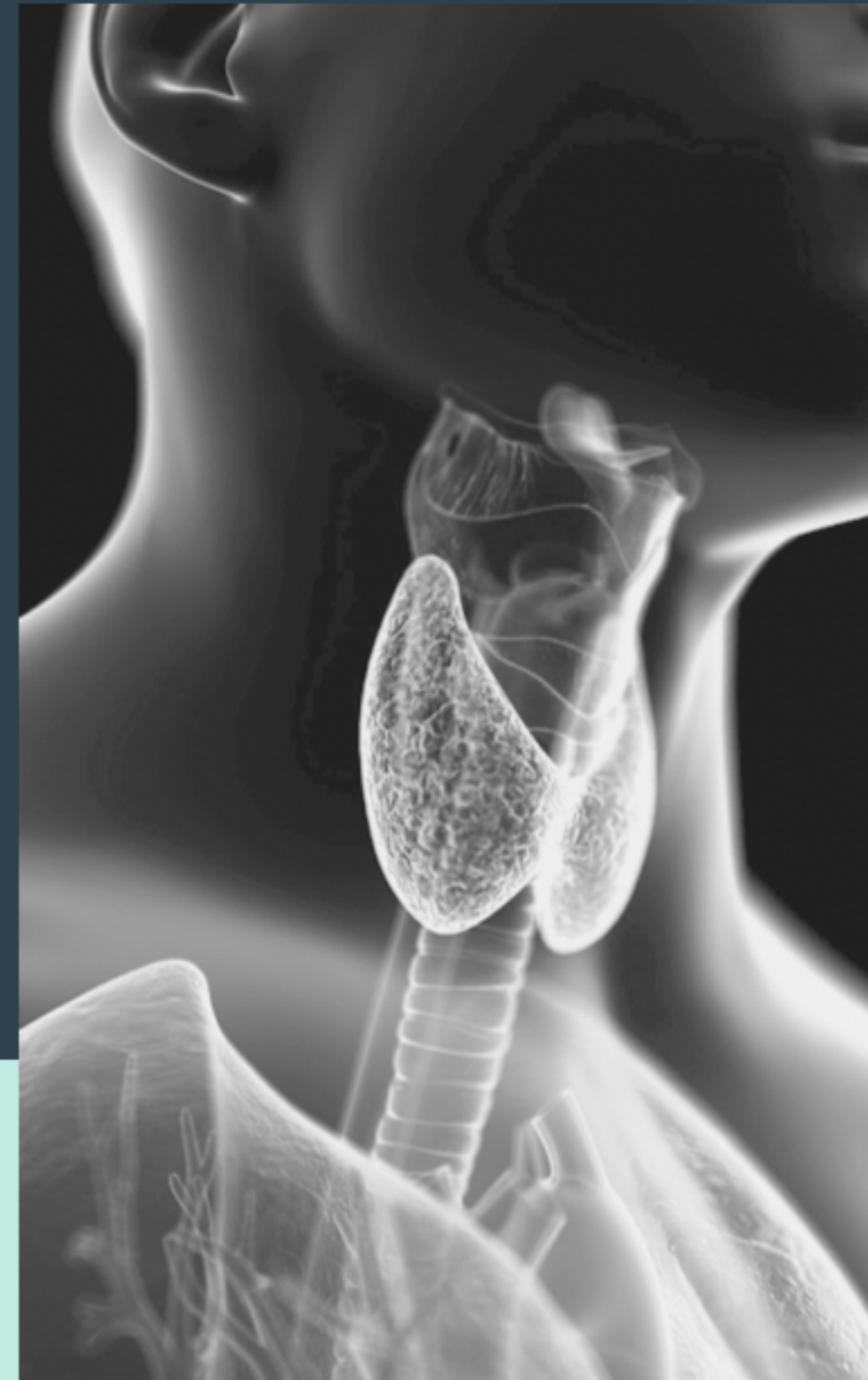
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Resistance to Thyroid Hormone

F1 Apanaree Bhekasuta
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High TSH and high free T4 in adults*

Differential diagnosis:

- Nonadherence to treatment for hypothyroidism with increased intake of levothyroxine prior to blood sampling
- TSH-secreting pituitary adenoma
- Resistance to thyroid hormone
- Assay interference due to heterophilic antibodies or autoantibodies to TSH
- Amiodarone therapy (early in the course of therapy)



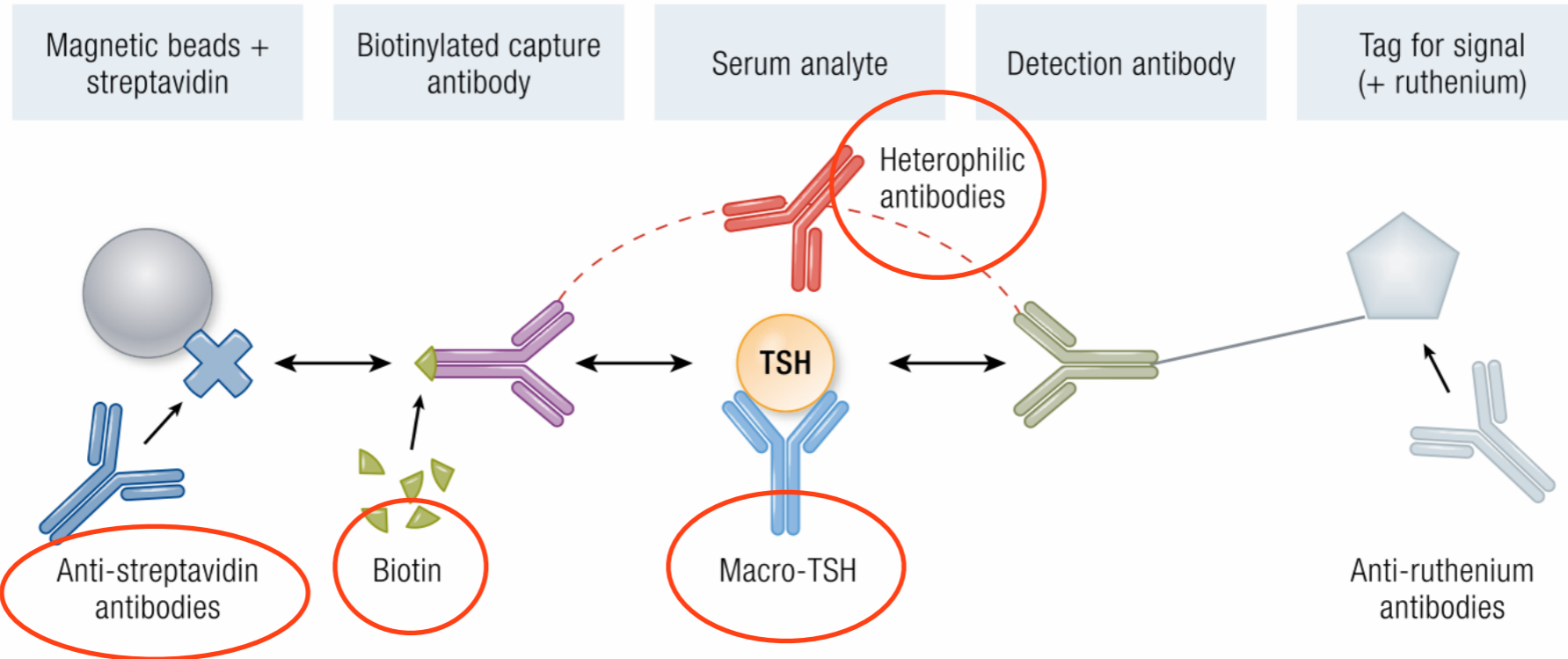
Measure:

- Repeat TSH
- Repeat free T4
- Total T3

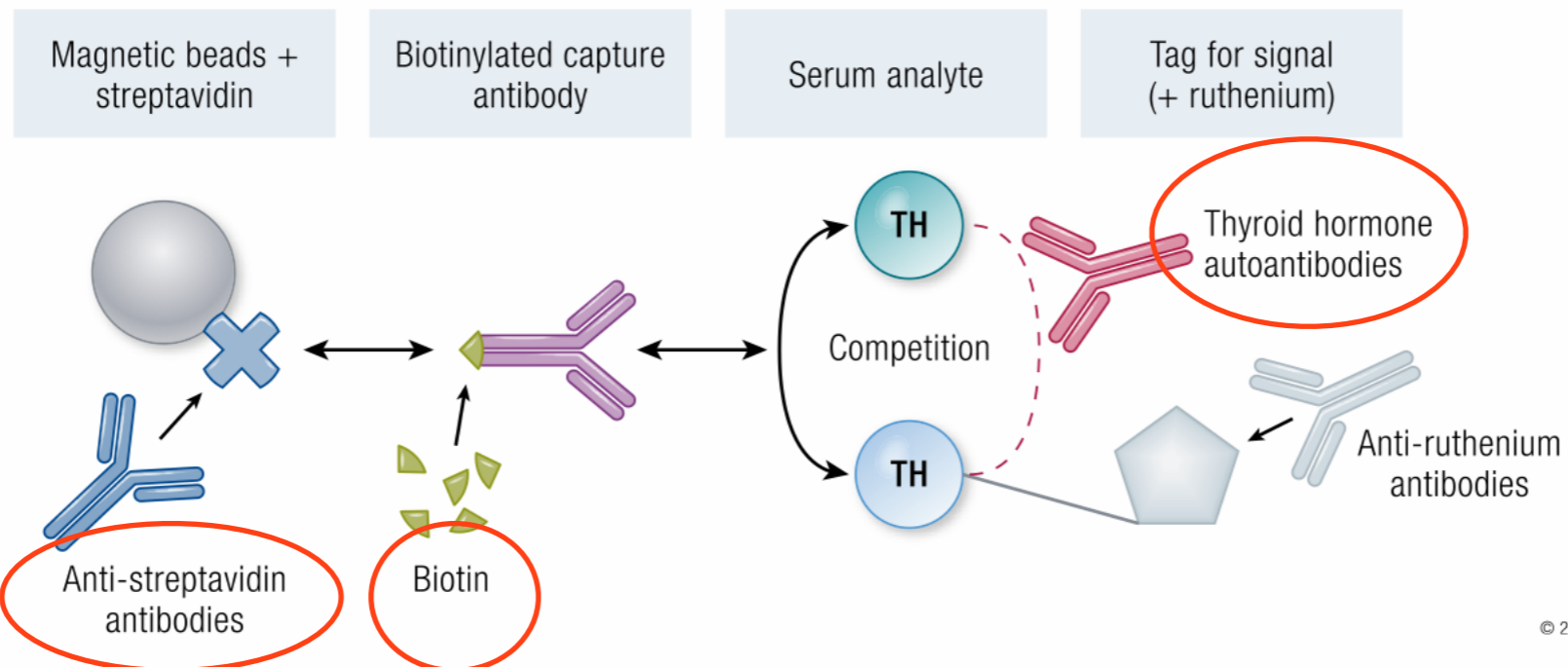
If abnormality persists, obtain endocrinology consult for further evaluation and management

Interferences

(a) Two-sites immunoassays (TSH)



(b) Competitive immunoassays (TH)



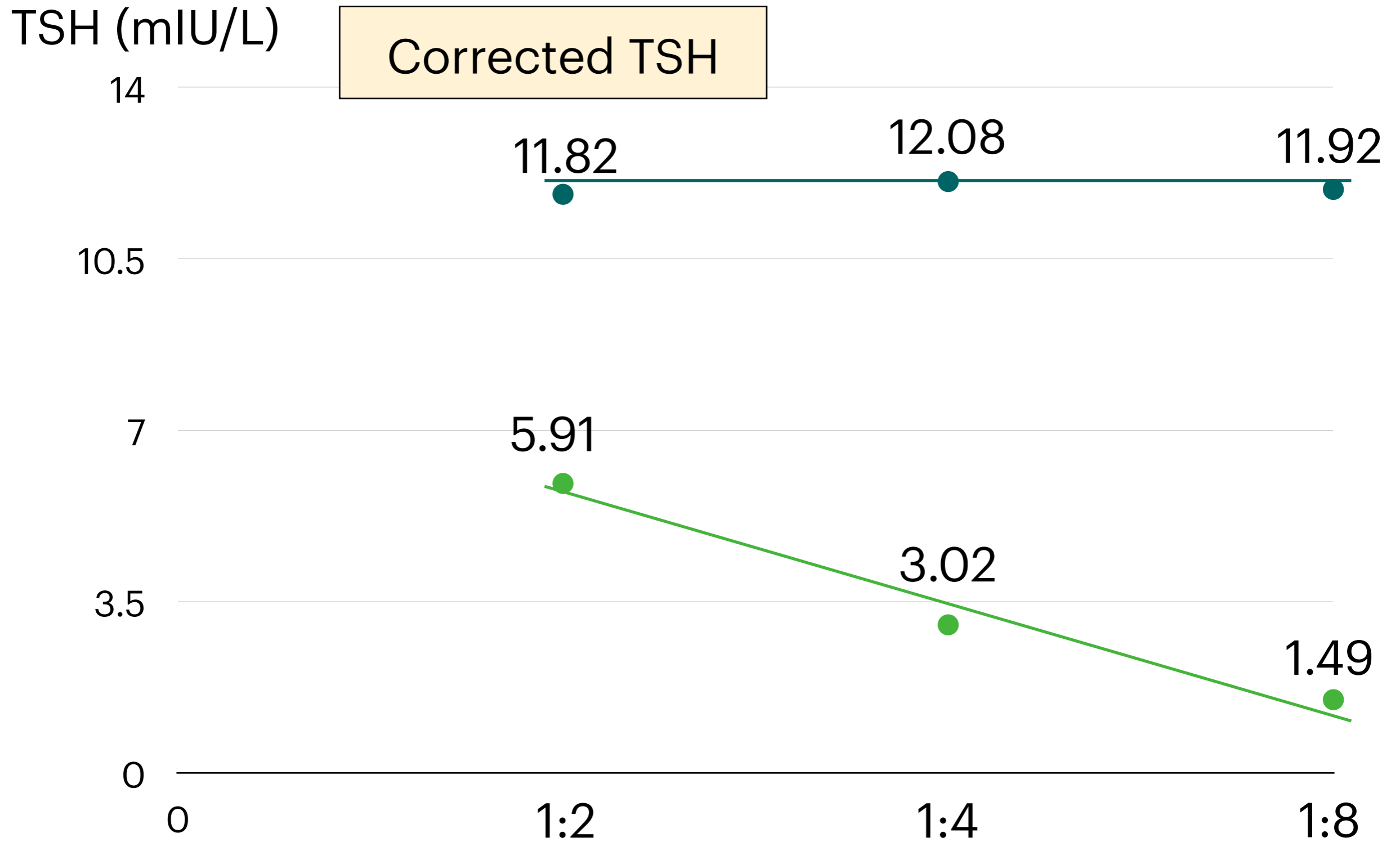
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Author (Ref)	Analyte(s) Affected	No.	Clinical Consequence	Methodology Used To Detect Interference ^a
Schaison <i>et al.</i> , 1981 (119)	↑ FT4	1	TRH and T3 administration (10 d)	Dilution test, method comparison, IE, ID, rabbit serum and Ig, immunonephelometric assay
Czernichow <i>et al.</i> , 1981 (114)	↑ TSH	14	¹²³ I scan with or without TRH test (8 patients/14)	Method comparison, dilution test, AC, ¹²⁵I-labeled rabbit IgG incubation (and PEG precipitation) (7 patients/14), rabbit Ig incubation
Gendrel <i>et al.</i> , 1981 (128)	↑ TSH	7	¹²³ I scan and TRH test (7 patients/7), L-thyroxine (up to 4 mo) (4 patients/7)	Dilution test, rabbit serum
Brennan <i>et al.</i> , 1987 (120)	↑ TSH	2	TRH test (2 patients/2) and L-thyroxine (increased doses and undesirable effects) (1 patient/2)	Dilution test, method comparison, incubation with high TSH sample, mouse serum, AE
Zweig <i>et al.</i> , 1988 (129)	↑ TSH	1	Rx L-thyroxine (increased doses)	Dilution test, method comparison, mouse Ig
Kahn <i>et al.</i> , 1988 (130)	↑ TSH	3	TRH test (2 patients/3) and L-thyroxine (3 patients/3)	EP, different species Ig/sera, method comparison, RF, dilution test, binding of ¹²⁵I-labeled TSH, immunoabsorption with mouse IgG-1
Harvey <i>et al.</i> , 1988 (131)	↑ TSH	1	Rx L-thyroxine (6 wk)	Method comparison, mouse serum
Wood <i>et al.</i> , 1991 (126)	↑ TSH	1	TRH test and L-thyroxine (2 mo)	Mouse Ig

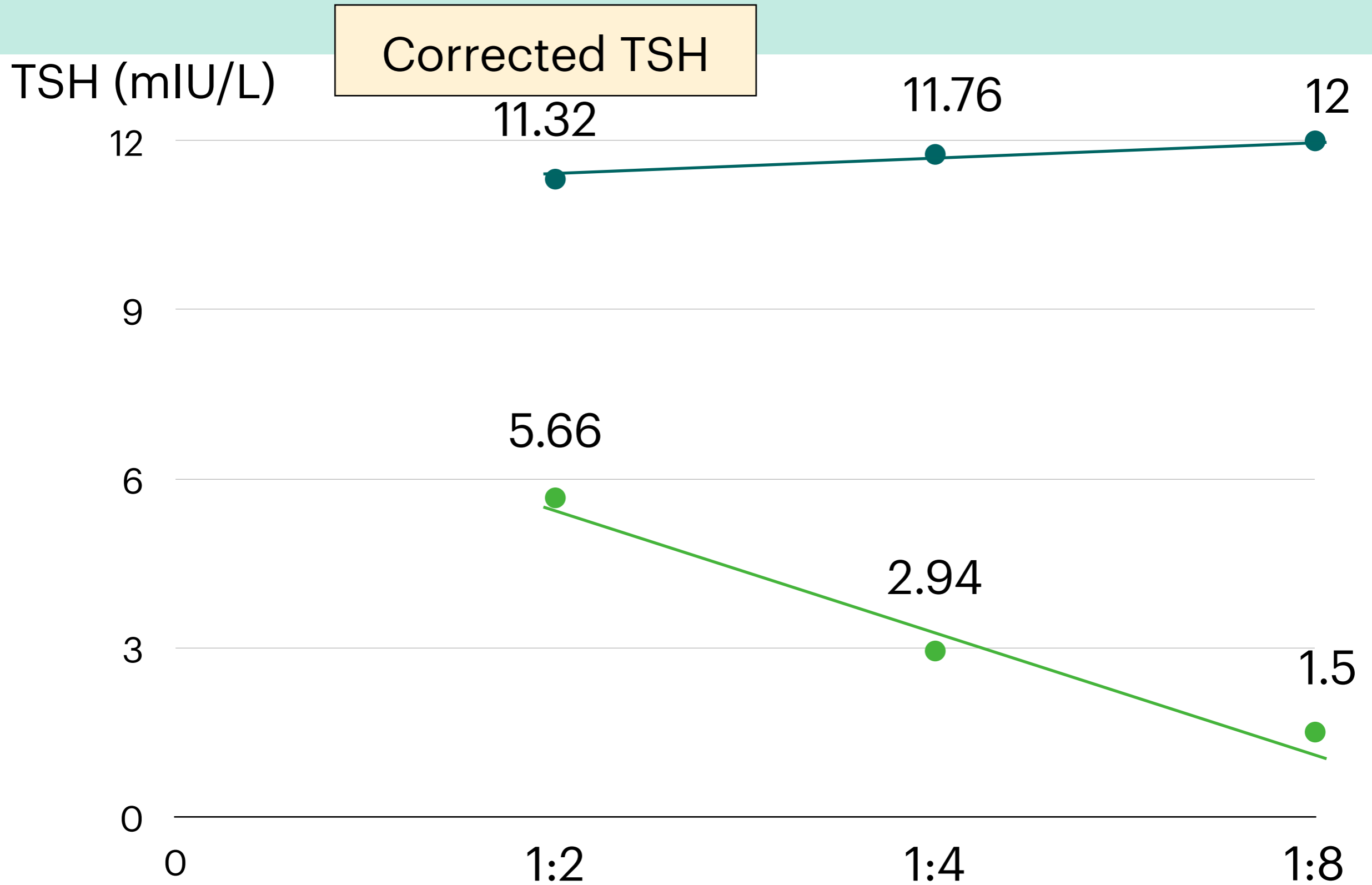
Method comparison, Dilution test, Blocking tube

Santhana Krishnan <i>et al.</i> , 2006 (123)	↑ TSH	1	L-thyroxine (with undesirable effects) and propranolol	Method comparison, mouse Ig
Monchamp <i>et al.</i> , 2007 (112)	↑ FT4/3	1	ND	Method comparison, dilution test, sheep Ig, HBT, AF, RF
Sapin <i>et al.</i> , 2007 (81)	↑ FT3	2	ND	Method comparison, HBT, ¹²⁵I-T3 precipitation
Ross <i>et al.</i> , 2008 (133)	↑ TSH	2	ND	Dilution test, HBT, method comparison, AC
Chin <i>et al.</i> , 2008 (127)	↑ TSH, FT4/3	1	Discontinuation of antithyroid drugs	Method comparison, dilution test, HBT, RF
Ghosh <i>et al.</i> , 2008 (121)	↑ FT4	2	Rx carbimazole (1 patient/2)	Method comparison
Saleem <i>et al.</i> , 2009 (134)	↑ FT4	1	Discontinuation of L-thyroxine (symptoms of hypothyroidism)	Method comparison, RF, protein A treatment, HBT
Verdictt <i>et al.</i> , 2012 (125)	↑ TSH	1	Rx L-thyroxine (increased doses)	EP, HBT, method comparison
Morton, 2014 (122)	↑ TSH	1	Rx L-thyroxine (increased doses for 2 y)	HBT
Hattori <i>et al.</i> , 2015 (14)	↑ TSH	1	ND	PEG, GFC, adsorption of serum IgG, dilution test, HAMA blockers
Gulbahar <i>et al.</i> , 2015 (135)	↑ TSH	1	Rx L-thyroxine	Method comparison, dilution test, HBT, RF, PEG
Soleimanpour <i>et al.</i> , 2015 (124)	↑ TSH	1	Delayed diagnosis of thyroid storm	HAMA blockers
Revet <i>et al.</i> , 2016 (136)	↑ FT4	2	Decreased L-thyroxine doses (1 patient/2)	Method comparison, adsorption of serum IgG, HAMA blockers, HBT

Dilution Test with NSS



Dilution Test with TSH suppressed serum



Impaired sensitivity to thyroid hormone

previously known as reduced sensitivity to thyroid hormone

“Any process that interferes with the effectiveness of thyroid hormone and includes defects in thyroid hormone action, transport, or metabolism”

Impaired sensitivity to thyroid hormone

- Thyroid hormone cell membrane transport defect (THCMTD)

- Thyroid hormone metabolism defect (THMD)

- Thyroid hormone action defects

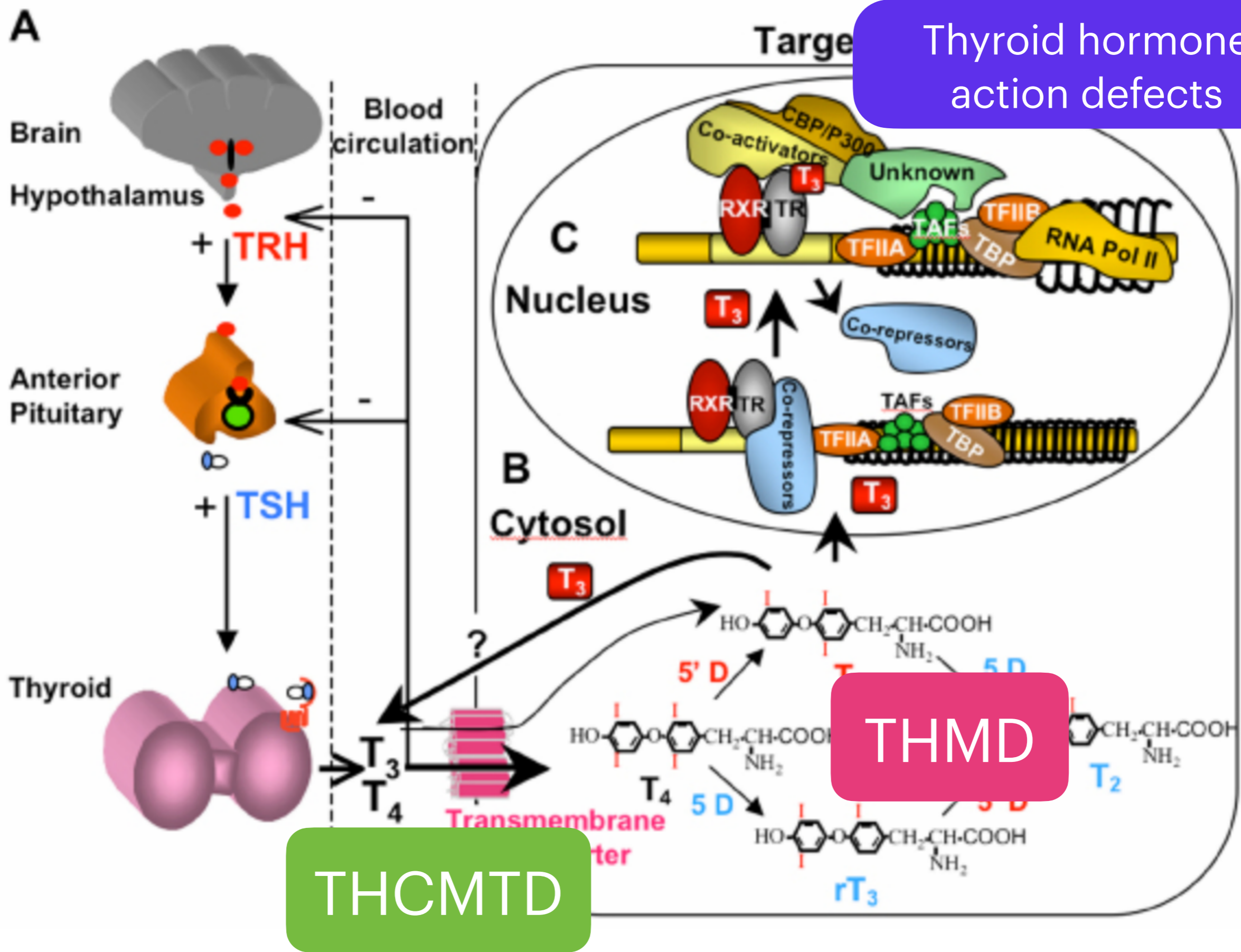
- RTH

- RTH-beta(TR-beta gene defects)

- NonTR-RTH(RTH of unknown etiology)

- RTH-alpha

Thyroid hormone action defects



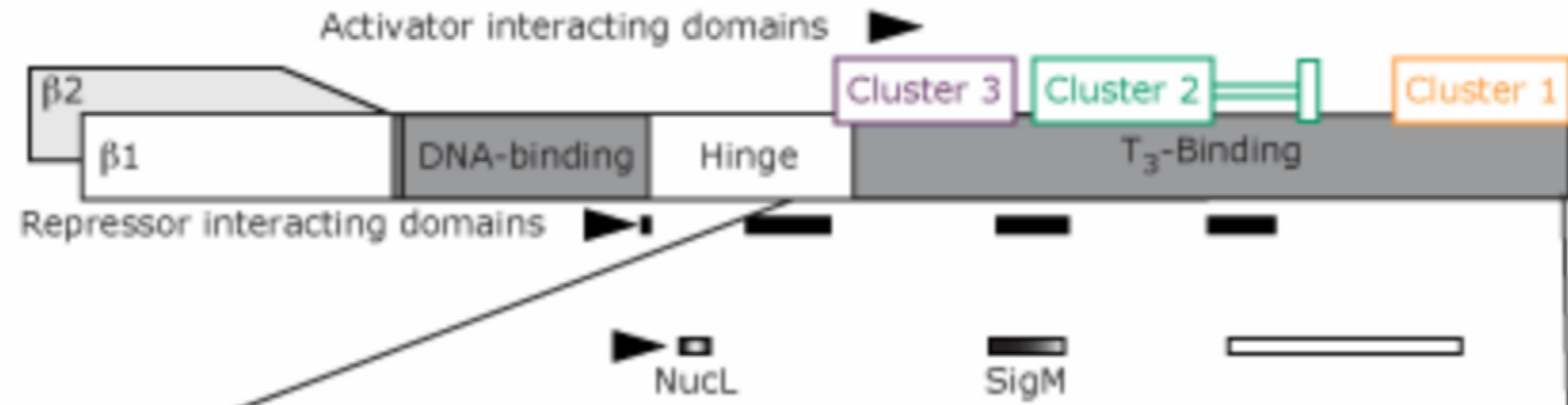
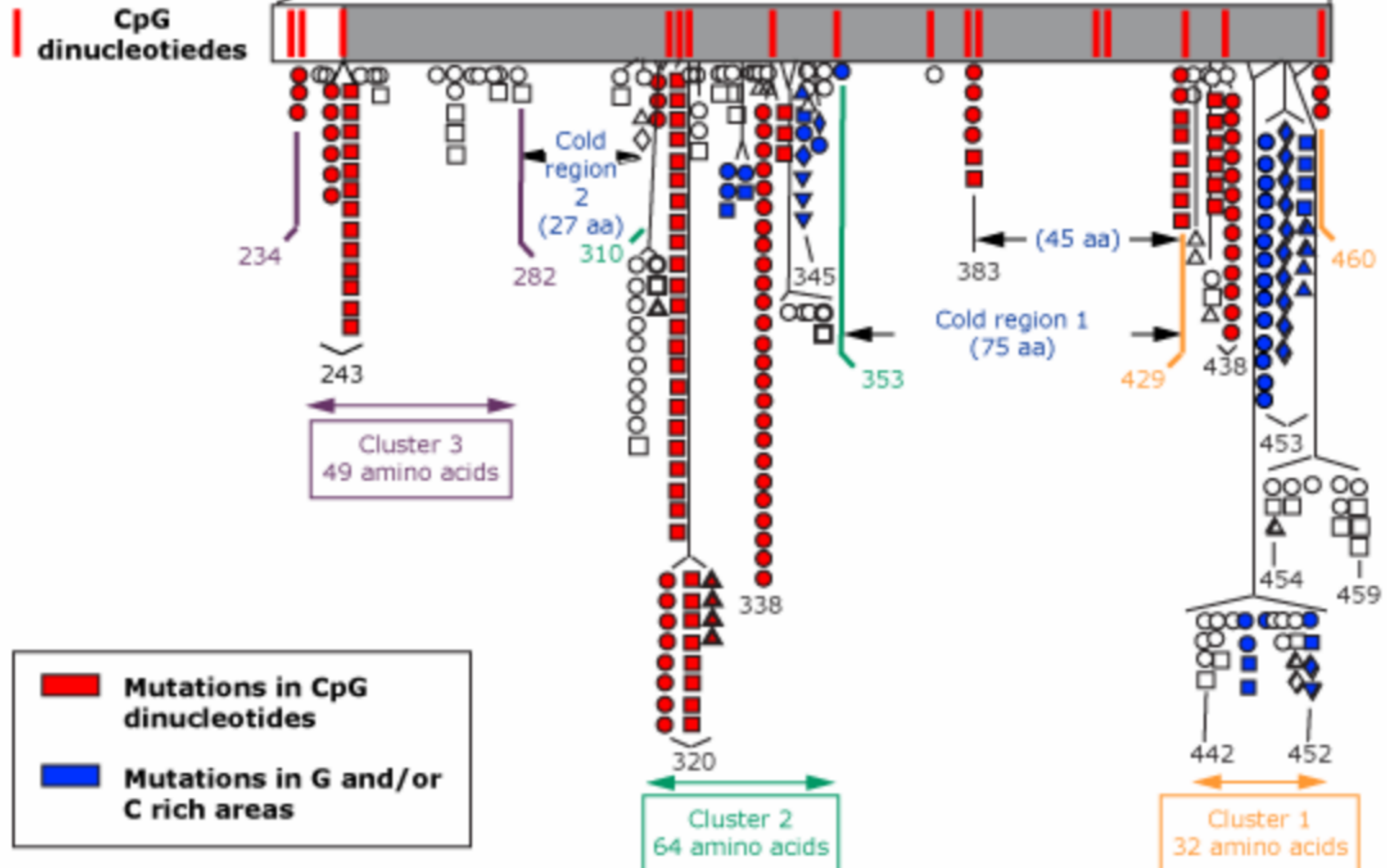
Reproduced with permission from: Refetoff, S, Dumitrescu, A. Syndromes of reduced sensitivity to thyroid hormone: genetic defects in hormone receptors, cell transporters and deiodination. Best Pract Res Clin Endocrinol Metab 2007; 21(2):277. Copyright ©2007 Elsevier. Illustrations used with permission of Elsevier, Inc. All rights reserved.

Comparison of TFT abnormalities in syndromes of impaired sensitivity to thyroid hormone

Syndrome	Gene	FT4	FT3	rT3	TSH	Other manifestations
THCMTD	<i>MCT8</i> (<i>SLC16A2</i>)	↓	↑↑	↓	N, sl ↑	Severe psychomotor impairment. Virtually all affected individuals are male.
THMD	<i>SBP2</i> (<i>SECISBP2</i>)	↑↑	↓	↑↑	N, sl ↑	Growth delay
Thyroid hormone action defects						
RTH-beta	TR-beta (<i>THRB</i>)	↑↑	↑ N	↑↑	N, sl ↑	ADD, tachycardia, goiter
NonTR-RTH	Unknown					
RTH-alpha	TR-alpha (<i>THRA</i>)	↓	N, sl ↑	↓	N	Delayed skeletal development Gastrointestinal dysmotility

Resistance to Thyroid Hormone-beta

- Inherited syndrome characterised by reduced responsiveness of target tissues to thyroid hormone
- High serum concentrations of FT4 and usually FT3, accompanied by normal or slightly high TSH concentrations
- Prevalence: 1 of 40,000 live births
- Autosomal Dominant
- *THRB* gene(chromosome 3)

A**B**

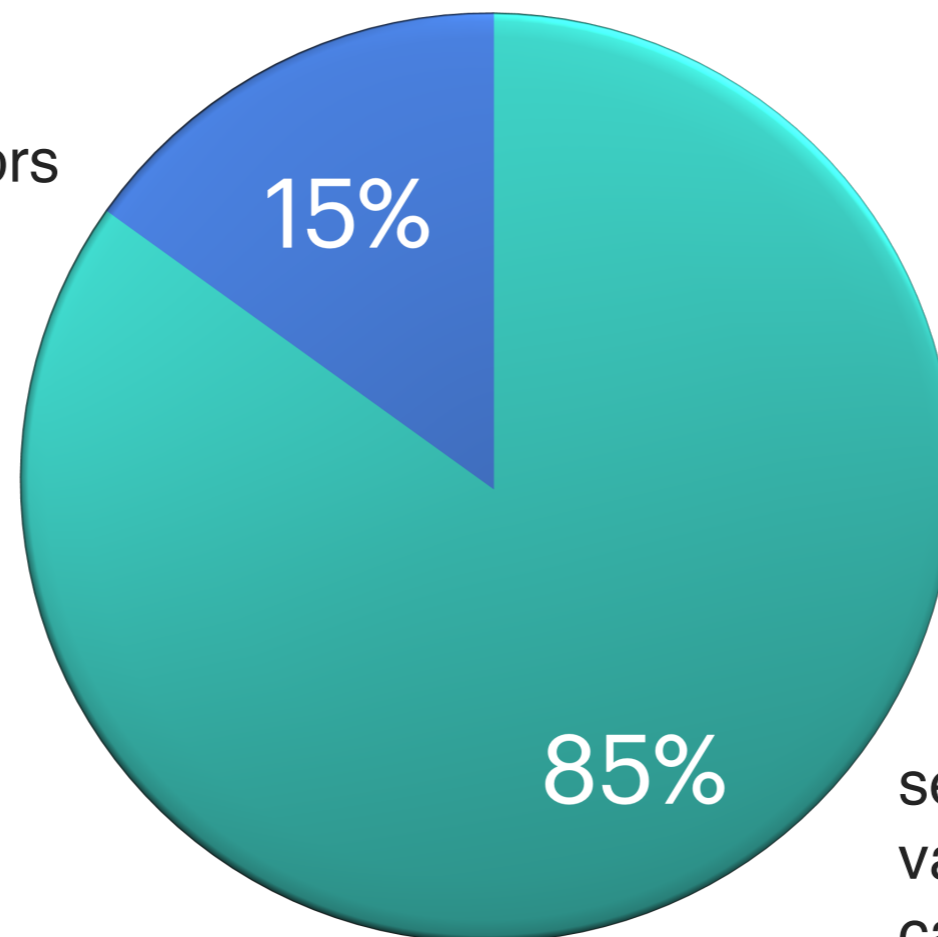
Kindred*	Sex of index case	Age of index case at presentation <i>yr</i>	FT ₄ (9.0–20 pmol/liter)	FT ₃ (3.0–7.5 pmol/liter)	TSH (0.4–4.0 mU/liter)	Phenotype	Inheritance [‡]	Nucleotide change	Exon	Codon change [§]	K _a /10 ¹⁰ M ⁻¹ (SEM) WT = 2.2 (0.2)	Members analyzed [¶]
G. P.	M	23	29	15	2.5	GRTH	Sp	1076 GTT to GAT	8	V264D	< 0.02	1A, 4U
deG.	F	22		See Table III		GRTH	F	1232 CGC to CAC	9	R316H	< 0.02	3A, 1U
C. M.	F	22	53	16	1.5	GRTH	F	1234 GCT to ACT	9	A317T	0.28 (0.05)	2A, 1U
P. C.	F	12	23	16	2.3	GRTH	Sp	1234 GCT to ACT	9	A317T	0.28 (0.05)	2A, 6U
P. M.	F	11	29	9	2.0	GRTH	F	1244 CGC to CAC	9	R320H	0.83 (0.12)	3A, 4U
S. C.	F	31	34	14	4.2	GRTH	F	1244 CGC to CTC	9	R320L	0.21 (0.06)	5A, 1U
G. M.	M	37	40	11	3.6	PRTH	F	1244 CGC to CTC	9	R320L	0.21 (0.06)	2A, 1U
S. T.	F	13	49	14	2.1	PRTH	F	1247 TAT to TGT	9	Y321C	0.04 (0.02)	2A, 5U
B. B.	M	25	46	18	6.9	GRTH	F	1280 GGG to GAG	9	G332E	0.04 (0.01)	2A, 3U
J. M.	M	14	71	13	4.1	PRTH	F	1297 CGG to TGG	9	R338W	0.21 (0.06)	2A, 2U
R. M.	F	28	16	6	185	PRTH	Sp	1297 CGG to TGG	9	R338W	0.21 (0.06)	1A, 4U
L. M.	F	31	36	8	1.4	GRTH	F	1297 CGG to TGG	9	R338W	0.21 (0.06)	3A, 5U
N. M.	F	9	28	13	2.4	PRTH	F	1298 CGG to CTG	9	R338L	0.57 (0.13)	2A, 2U
B. K.	M	16	64	16	4.1	GRTH	NK	1316 GGG to GAG	9	G344E	BND	1A, 3U
S. S.	F	41	44	14	2.5	PRTH	NK	1330 CTG to ATG	9	V349M	0.51 (0.04)	1A, 3U
M. S.	F	41	27	15	1.1	PRTH	NK	1571 CGG to CAG	10	R429Q	0.46 (0.11)	1A, 1U
M. A.	M	34	31	12	7.8	GRTH	F	1571 CGG to CAG	10	R429Q	0.46 (0.11)	2A
L. O.	F	2	25	9	1.4	PRTH	Sp	1577 ATA to ACA	10	I431T	0.02 (0.01)	1A, 4U
C. Ma.	M	37	25	12	5.6	GRTH	F	1597 CGC to TGC	10	R438C	0.67 (0.15)	2A, 1U
B. W.	M	42	36	12	2.7	GRTH	F	1598 CGC to CAC	10	R438H	0.51 (0.20)	5A, 3U
C. S.	M	55	39	11	5.8	GRTH	NK	1598 CGC to CAC	10	R438H	0.51 (0.20)	1A
G. S.	F	54	46	17	1.5	GRTH	NK	1598 CGC to CAC	10	R438H	0.51 (0.20)	1A, 2U
J. H.	M	35	35	13	1.5	GRTH	F	1598 CGC to CAC	10	R438H	0.51 (0.20)	5A
S. N.	F	17	69	17	2.2	GRTH	F	ACTCTTC 1638i	10	fs 452	BND	3A, 1U
S. H.	F	25	35	13	3.3	GRTH	Sp	1642 CCT to ACT	10	P453T	0.44 (0.08)	1A, 2U
P. A.	F	28	44	10	2.0	GRTH	F	1642 CCT to ACT	10	P453T	0.44 (0.08)	2A, 1U
M. C.	F	22	35	12	1.5	GRTH	F	1642 CCT to TCT	10	P453S	0.79 (0.19)	3A, 2U
T. B.	M	45	25	22	1.9	PRTH	NK	1642 CCT to GCT	10	P453A	0.38 (0.03)	1A, 5U
M. P.	F	35	9	11	5.0	GRTH	F	1663 GAG to AAG	10	E460K	0.55 (0.14)	2A, 1U

Resistance to Thyroid Hormone

- The severity of hormonal resistance varies among different tissues in an affected individual
- Due to differences in the relative expression of TR-beta and thyroid hormone receptor alpha (TR-alpha) in different tissues

NonTR-RTH

Mutations of one of the cofactors that interact with the receptors



RTH-beta

severity of hormonal resistance varies among different subjects carrying the same gene mutation

Clinical features

Frequency of symptoms and signs in patients with resistance to thyroid hormone

	Findings	Frequency, percent
Thyroid gland	Goiter	66 to 95
Heart	Tachycardia	33 to 75
Nervous system	Emotional disturbances	60
	Hyperkinetic behavior	33 to 68
	ADHD	40 to 60
	Learning disability	30
	Mental retardation (IQ <70)	4 to 16
	Hearing loss (sensorineural)	10 to 22
Growth and development	Short stature (<5%)	18 to 25
	Delayed bone age >2 SD	29 to 47
	Low BMI (in children)	33
	Recurrent ear and throat infections	55

ADHD: attention deficit hyperactivity disorder; IQ: intelligence quotient; SD: standard deviation; BMI: body mass index.

Investigation

- The abnormalities should be confirmed by **repeat measurements** several weeks later
- **Exclude** condition associated with hyperthyroxenemia

Thyroid function tests							
Defect	T ₄	T ₃	rT ₃	TSH	FT ₄ direct	FT ₄ dialysis	Prevalence*
Increased T4-binding globulin	↑	↑	↑	N	N	N	Common
Increased transthyretin [¶]	↑	N	↑	N	N	N	Rare
FDH	↑	↑ or N	↑	N	↑	N	Rare or common ^Δ
RTH (usually due to a mutation in the TR-beta gene [RTH-beta])	↑	↑ or N	↑	sl ↑ or N	↑	↑	Uncommon
TSH-producing pituitary adenoma	↑	↑	↑	sl ↑ or N	↑	↑	Rare
SBP2/SECISBP2 mutation (causes a thyroid hormone metabolism defect)	↑	↓	↑	sl ↑ or N	↑	↑	Unknown
Acute nonthyroidal illness	↑	↓↓	↑	N	↑ or N	N	Common

Investigation

- Genetic testing (*THRB* gene)
- Dynamic testing (Individuals without an identifiable *THRB* gene mutation but with thyroid function tests consistent with RTH-beta may have nonTR-RTH)
 - TRH stimulation test
 - T3 suppression test
 - Somatostatin Suppression test

Treatment

- Symptomatic treatment:
 - Heart rate/rhythm control: Beta blocker
 - Avoid ATD and I-131
- LT4 treatment
 - In hyporesponsive organ, growth, bone maturation, mental development
- Thyroid hormone analog: triiodothyroacetic acid
 - Limited beneficial effect and not available

Triiodothyroacetic acid

- In a subgroup of RTH β patients, TA3 is able to decrease TSH and consequently the high serum T4 and T3 levels.
- Since the thyromimetic effects of TA3 itself do not fully compensate the reduction in endogenous TH levels
- Alleviates the thyrotoxic symptoms including tachycardia, goiter, excessive sweating and behavioral problems