THE UNIVERSITY OF CHICAGO MEDICINE & BIOLOGICAL SCIENCES

"Two infants with congenital hypothyroidism (CH): same problem for a different reason "

Samuel Refetoff

ENDORAMA
October 22, 2020

Dr. Refetoff does not have any relevant financial relationships with any commercial interests.

Congenital Hypothyroidism (CH)

Incidence: 1 in 1,500 to 4,000

Phenotypes		**Genetic Defects**
Dysgenesis (athyreosis, ectopy, hypoplasia)	**80%**	*PAX8, TTF1, TTF2, TSHR, TSHß*
Dyshormonogenesis	**15%**	*NIS, TPO, Pendrin, TG, DUOX2 DUOXA2, SLC26A7, DEHAL1*
Selective Tissue Abnormalities (syndromic)		*THRA, THRB, MCT8, SBP2, DIO1*
Multiple hormone deficiencies (Pituitary transcription factors)		*PIT1. PROP1, HESX1, LHX3, LHX4*

CASE 1

James Amrhein May18, 2020 at 6:07 PM

To: Samuel Refetoff, MD Cc: Beth Weir
Newborn with congenital hypothyroidism and resistance to thyroid hormone

Dear Dr Refetoff
I am reaching out to you about a very confusing and concerning baby boy with congenital hypothyroidism who appears to have significant resistance to thyroid hormone also. You can see my note to Steve Lafranchi who as you know is probably the preeminent expert in our pediatric endocrine Society on thyroid disorders in children. This child's laboratory picture initially suggested severe congenital hypothyroidism. However, he has not responded to increasing doses of L-thyroxine as expected. Even with supraphysiologic levels of T4 and T3 we cannot suppress his TSH to anywhere near normal levels. Both Steve and I think he has 2 diseases-namely, congenital hypothyroidism and RTHbeta. You have previously helped me about 10 years ago by genetic analysis of a family with RTH. I have 2 questions for you. Have you ever seen concurrence of severe congenital hypothyroidism with RTH? And secondly would you be interested in blood for genetic analysis on this baby and his parents?

As you can see, this child is nearing the 6-month mark and I am very concerned about our inability to suppress his TSH to normal given the traditional statement that unsuppressed TSH in severe congenital hypothyroidism leads to adverse neurocognitive

Family

Severe congenital hypothyroidism requiring high doses of L-T4; Does she have also RTHß?

Proband R7429 5 mo: Full term in NICU for few days because of respiratory distress

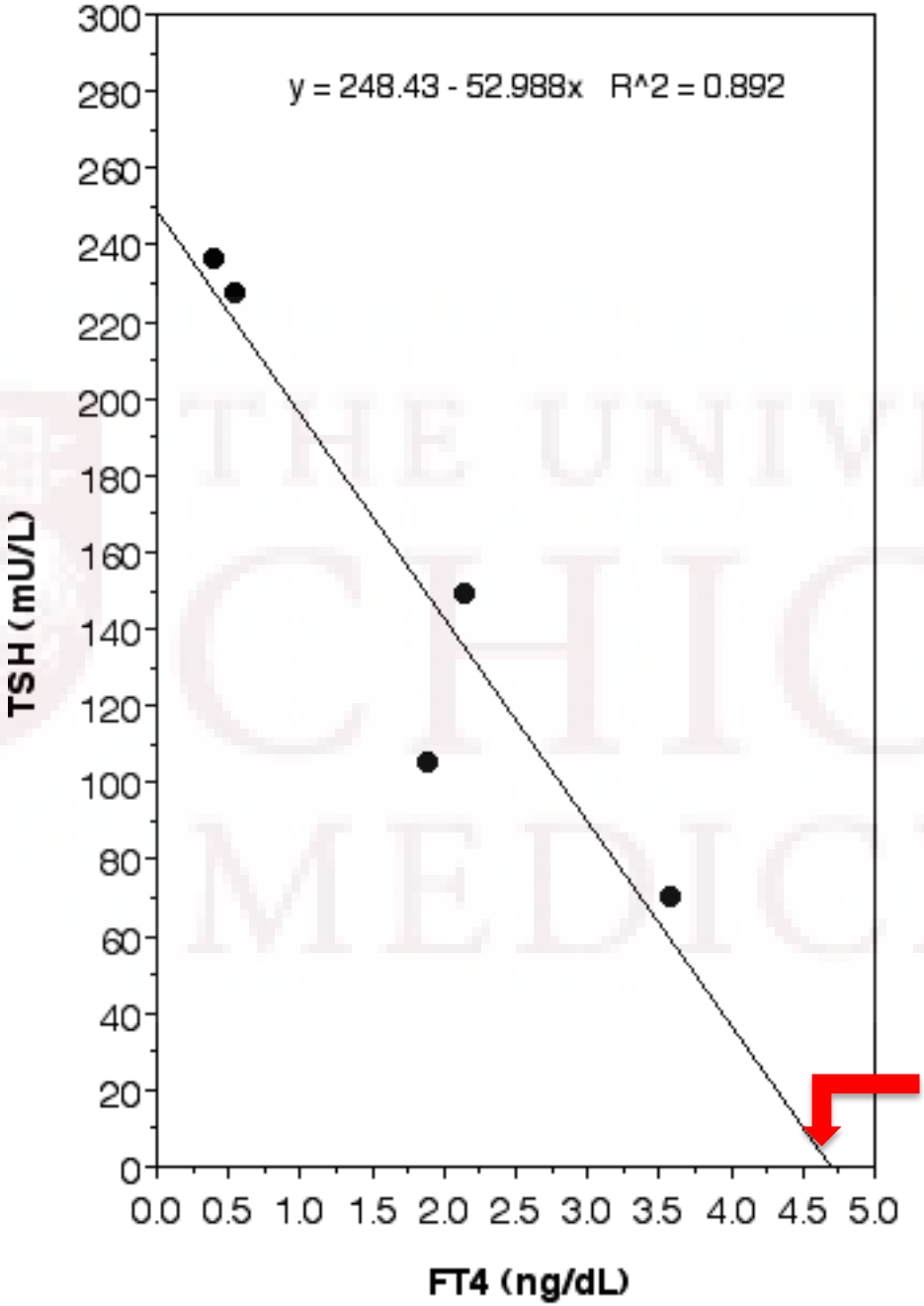
Question should the goal of treatment be to normalize the TSH or maintain FT4 in the upper limit of normal?

- **12/16/19 DOB: NBS- TSH- 378.49**
- **12/20/19- TSH- 235.6, free T4- <0.4- compounded thyroxine 44 mcg started**
- **12/25/19- TSH- 148.5, free T4- 2.15- decreased thyroxine to 37.5 mcg**
- **12/30/19- TSH- 70.3, free T4- 3.59- stopped thyroxine**
- **1/21/20- TSH- 227.3, free T4- 0.55- restart Synthroid 50 mcg po daily**
- **2/6/20- TSH- 104.6, free T4- 1.9- increased Synthroid 75 mcg po daily**
- **2/27/20- TSH- 59.8, free T4- 2.34- increase thyroxine to 100 mcg po daily**

James A. Amrhein, MD
Professor of Pediatrics, USC School of Medicine Greenville Campus Pediatric Endocrinology and Diabetes
Prisma Health–Upstate
200 Patewood Drive, Suite A320
Greenville, SC 29615
864-454-5162 (office)
864-363-1183 (mobile)
864-241-9238 (fax)

What would you like to know?

How would you proceed?



TG was undetectable when TSH was 62 mU/L indicating athyreosis.

Target T4 to normalize TSH

SMITH, SPENCER 975398006

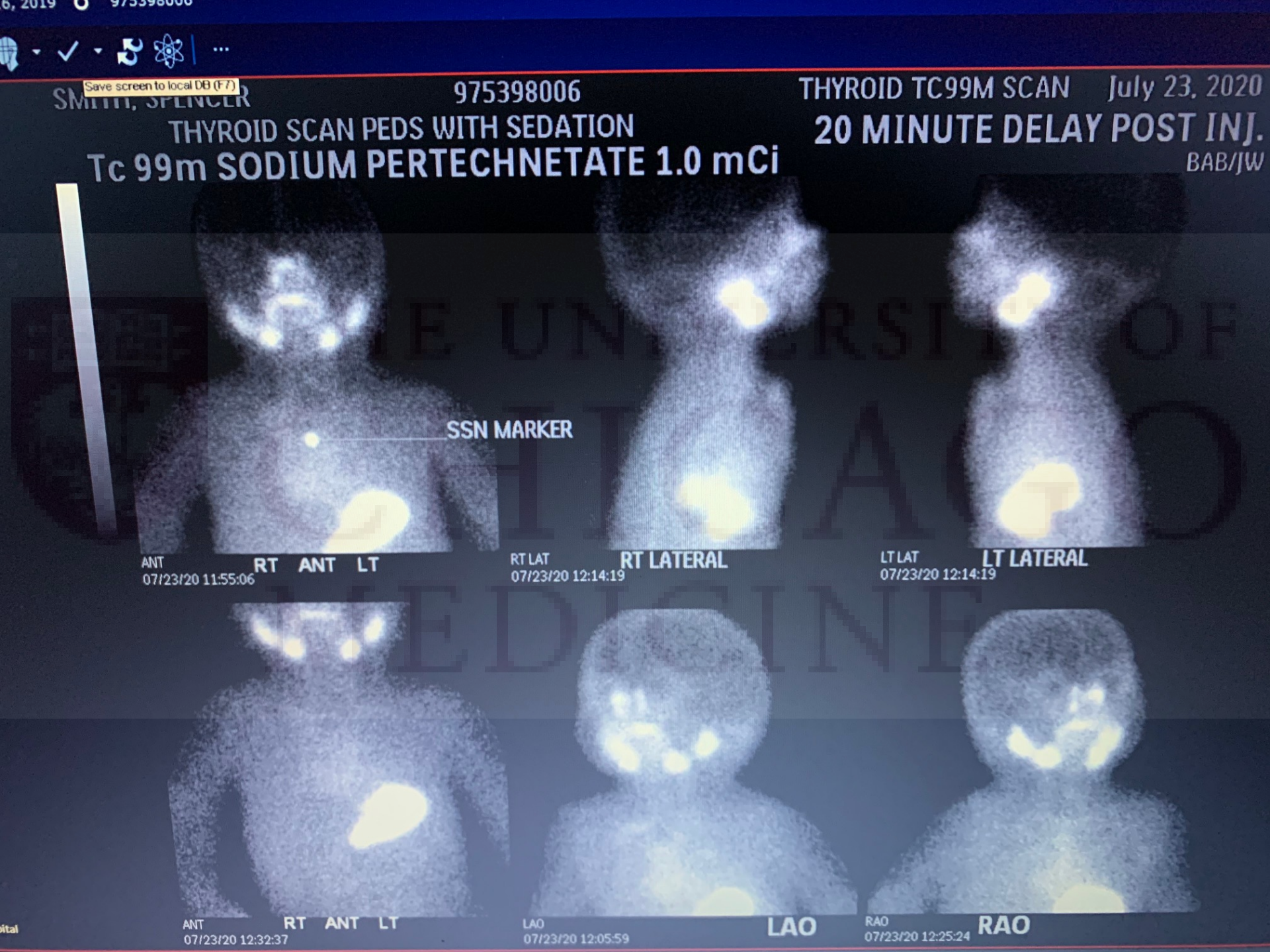
THYROID SCAN PEDS WITH SEDATION

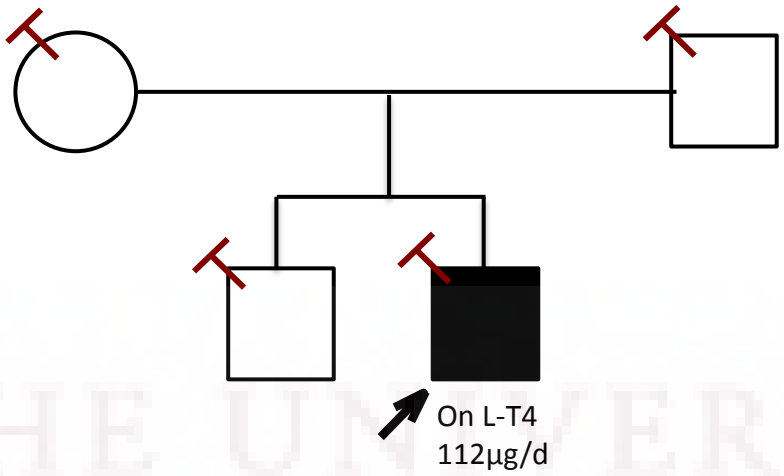
Tc 99m SODIUM PERTECHNETATE 1.0 mCi

THYROID TC99M SCAN July 23, 2020

20 MINUTE DELAY POST INJ.

BAB/JW





Legend

Proband

Tested

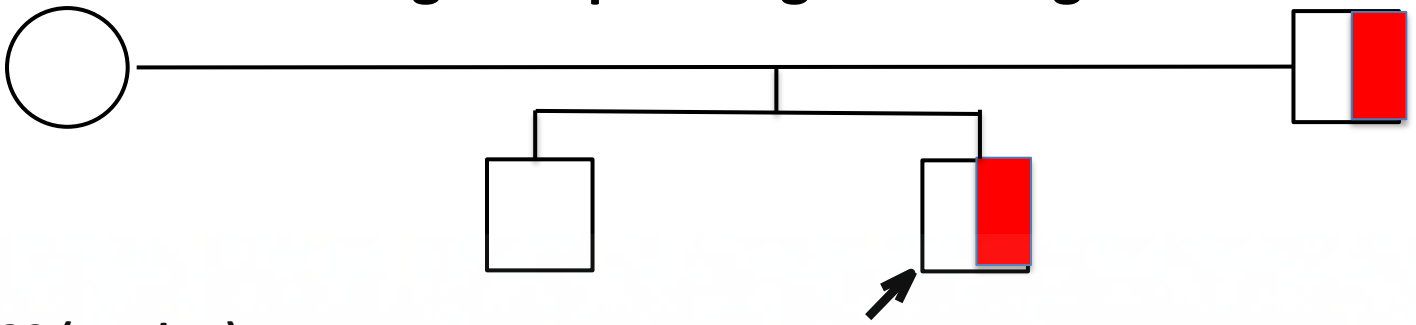
Abnormal values in **BOLD**

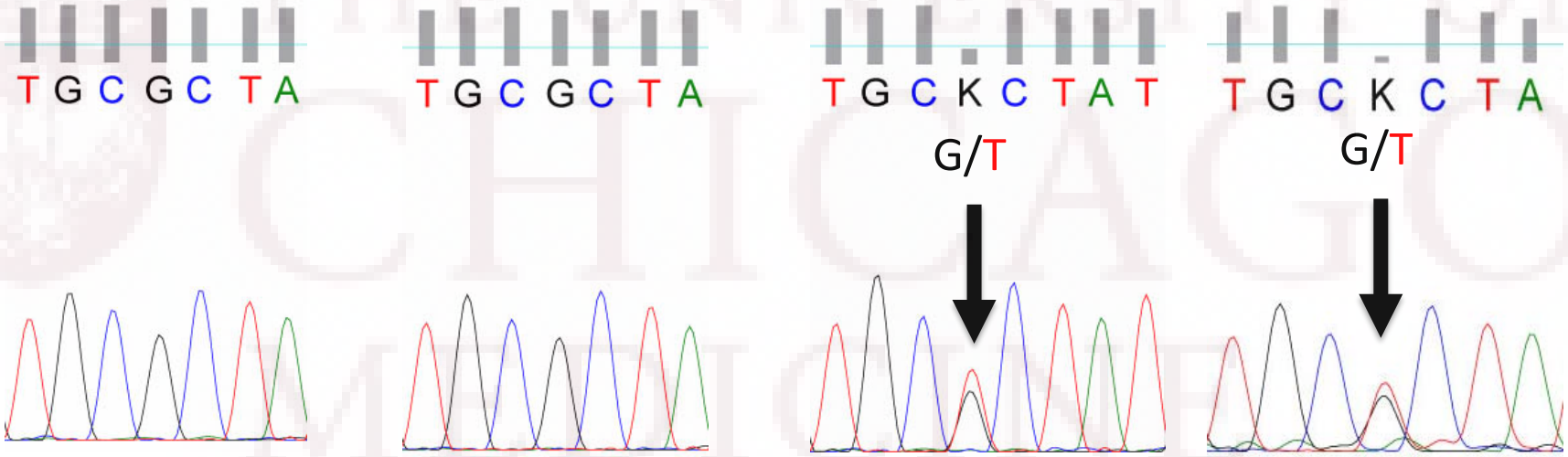
High in **RED**

Low in **BLUE**

	R7430	R7431	R7429	R7432	Reference range
Age (yrs)	**27**	**6**	**5 mo**	**37**	
TT4 (µg/dL)	4.8	6.0	**15.1**	8.3	5 - 12
TT3 (ng/dL)	93	146	197	119	80 - 190
TrT3 (ng/dL)	19.1	20.1	**151**	**47.6**	16 - 36
FT4 (ng/dl)	1.19	1.09	**2.44**	**2.05**	0.8 – 1.9
TSH (µIU/mL)	2.4	1.6	**61.9**	0.9	0.4 - 3.6
TG (ng/mL)	12	8	**<1**	39	2 - 38
TGab	<0.4	<0.4	<0.4	<0.4	<0.4
TPOab	<0.4	<0.4	<0.4	<0.4	<0.4

Sanger sequencing of *THRB* gene





Ka = 0.21 (WT Ka = 2.2) or **10% the WT**

First reported by Adams et al., 1994

Total families: 7

CGC -> CTC

Arg -> Leu

R320L

rs121908866; Polyphen 0.998.

Legend

Proband

Tested

Abnormal values in **BOLD**

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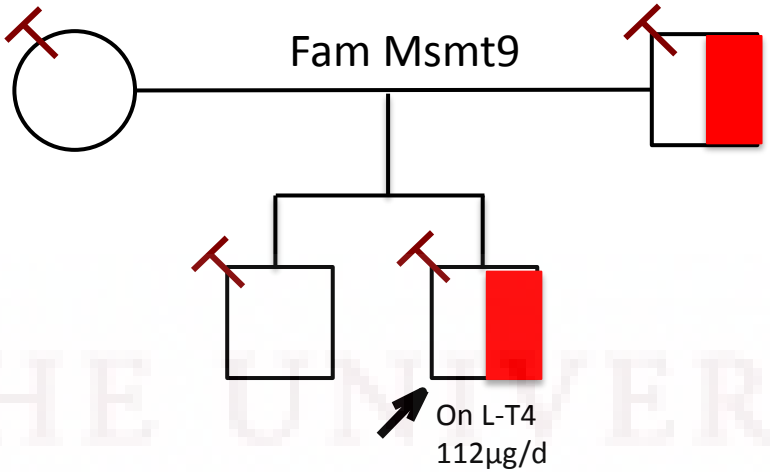
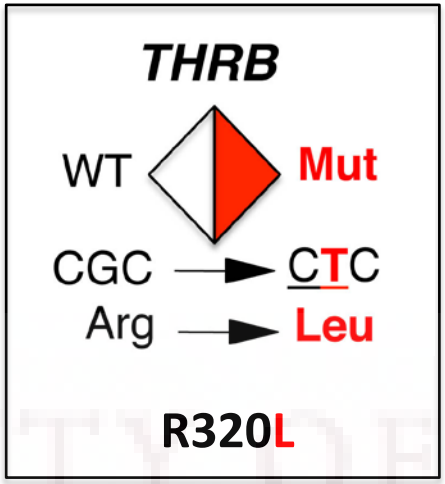
Low in **BLUE**





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TG (ng/mL)	12	8	**<1**	**39**	2 - 38
TGab	<0.4	<0.4	<0.4	<0.4	<0.4
TPOab	<0.4	<0.4	<0.4	<0.4	<0.4

At age 8 months; On 175 µg L-T4/ day

TSH 12 mU/L

TT4 23.5 µg/dl

FT4 4.0 ng/dl

TT3 264 ng/dl

rT3 95 ng/dl

Would you like to investigate further?

If so, how?

CASE 2

On Feb 1, 2016, at 9:01 PM, Shah, Amy <Amy.Shah@cchmc.org> wrote:

Dear Dr. Refetoff,

I am a colleague of Philippe Backeljauw in Cincinnati and he suggested I reach out to you regarding a thyroid case.
I have been following a 2 year old female from birth. It was a clear case of congenital hypothyroidism **TSH 457 with T4 of 1.9 mcg/dl** at birth. Well controlled on synthroid 25mcg to 37.5mcg for the first year of life.
Then started to show an elevation of her TSH but also T4 and free T4 (May 2015- see below). Our initial thought was non-compliance. Given the TSH elevation and mom promising no missed doses, I increased her dose a bit. T4 and free T4 got higher and eventually so high I was concerned she was hyperthyroid (July 2015- but TSH was normal). She was asymptomatic per mom and HR was normal. Because of high free T4 and T4- I decreased synthroid back to 37.5mcg and TSH is now 68 but T4 and free T4 remains high- high normal. Throughout all of this, normal weight gain and linear growth. There is no thyroid abnormalities in mom or dad.

I checked heterophilic Ab to look for TSH interference (HAMA)-negative
Send labs to ARUP to confirm and same results.
I am starting to wonder if she has partial thyroid hormone resistance in the setting of congenital hypothyroidism. Would be odd and found a few older articles in pubmed. OR maybe this is just non compliance?
Is there a way I could prove this?
Wondering if you had any other thoughts? Any other workup to be done?
Any help would be appreciated!

Thanks in advance.
Happy to speak by phone as well. My cell is 301-661-3911

Amy
Amy Sanghavi Shah MD MS
Assistant Professor, Endocrinology
Cincinnati Children's Hospital Medical Center

2 years old girl

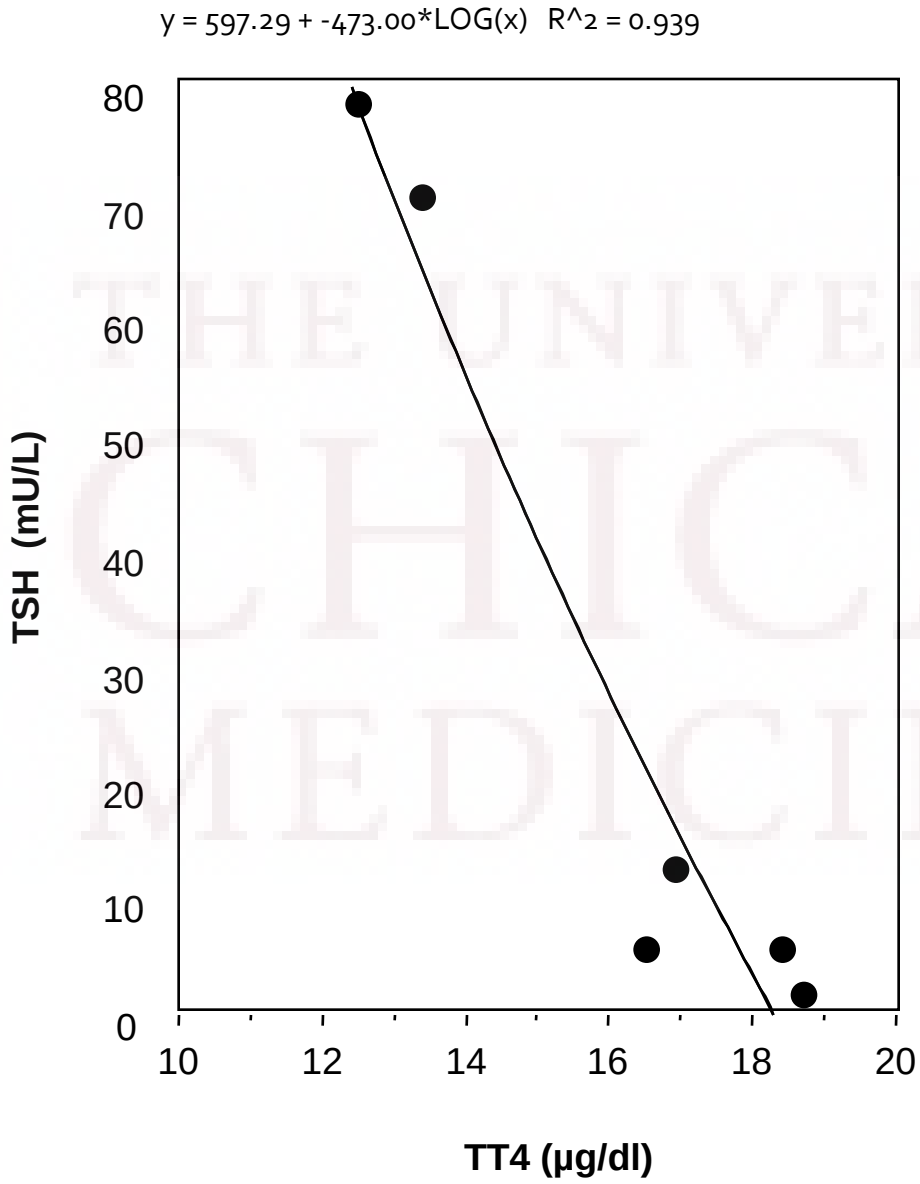
	Birth	2/16/15	5/21/15	7/1/15	7/17/15	8/27/15	10/19/15	1/3/16	1/21/16	2/8/16	normal
T3									1.24	1.08	0.92-2.1 ng/mL
T4	1.9	12.1	18.4	16.9	18.7	16.5	12.7		13.4	12.5	6.8-12.5 µg/dL
FT4 by direct dialysis				3.0	4.4	3.2	2.4	2.9		1.7	1-2.8 ng/dL
TSH	457	3.27	5.730	12.6	1.87	5.750		63.1	70.6	78.7	0.64-4.00 mU/mL
Synthroid (µg/day)		37.5	37.5	44	50	37.5	37.5	37.5	37.5	37.5	

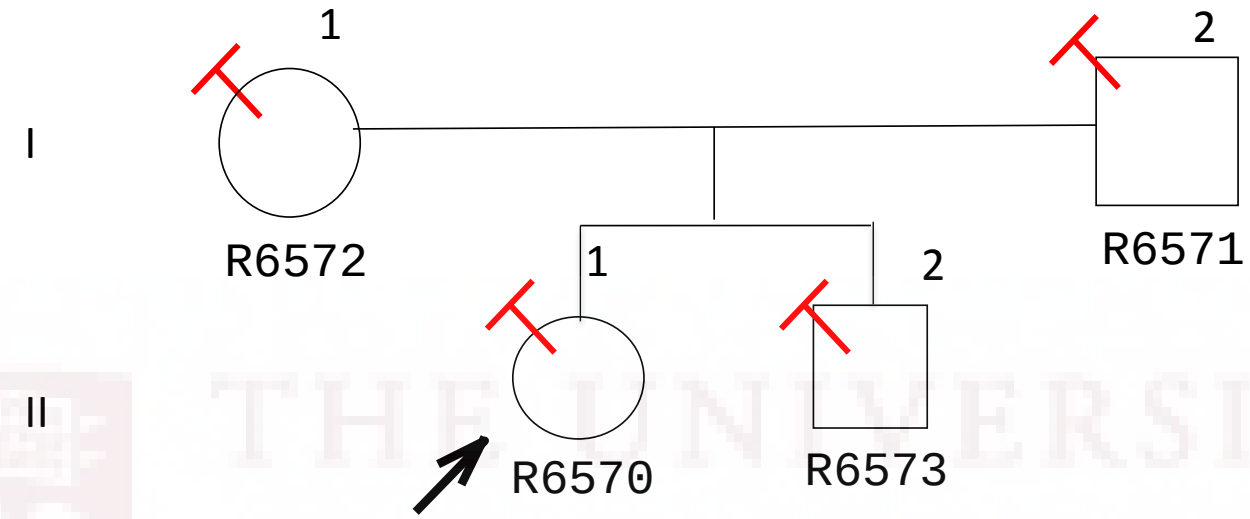
Dx: congenital hypothyroid (unknown cause)

- Good compliance
- Asymptomatic and normal HR
- Normal weight gain and linear growth
- No history of Biotin

What would you like to know?

How would you proceed?


y = 597.29 + -473.00*LOG(x) R^2 = 0.939
80
70
60
50
40
30
20
10
0
TSH (mU/L)
10
12
14
16
18
20
TT4 (µg/dl)

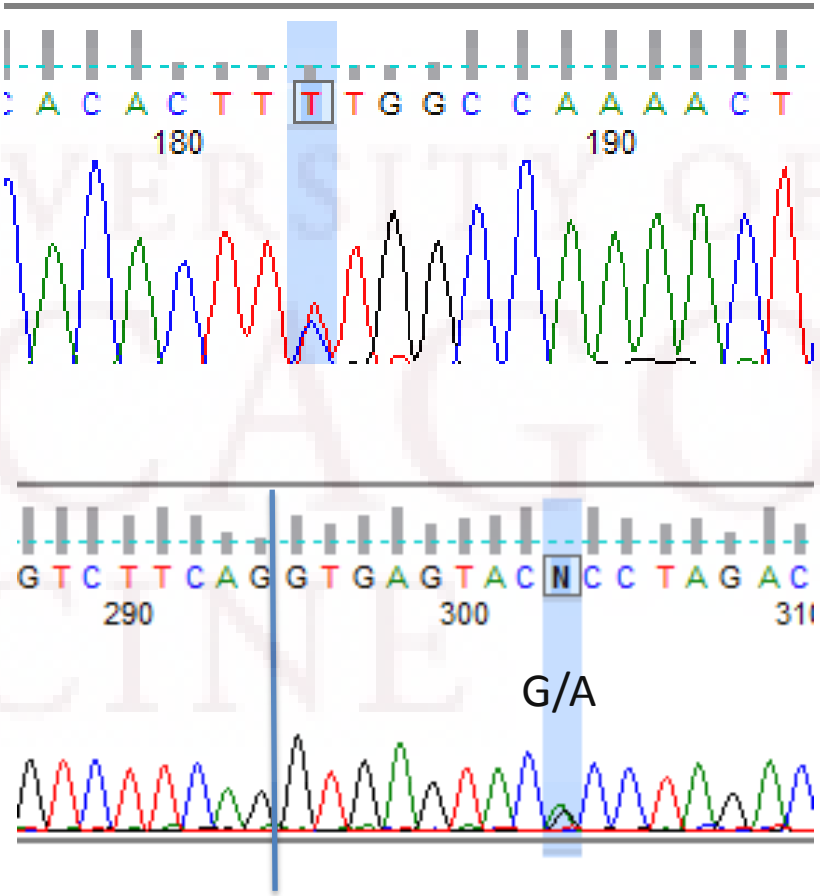


Abnormal values in **BOLD**
High in **RED,** low in **BLUE**
† normal for age

Age (years)	27	2.5	0.8	26	Reference range
TT4 ug/dl	7.6	11.6	8.3	7.4	5-11.6
TT3 ng/dl	107	105	151	114	90-180
TrT3 ng/dl	31.4	**65.7**	43.7†	28.0	16-36
FT4I	9	**12.2**	8.1	8.1	6.0-10.5
TSH uU/ml	2.2	**40**	3.5	0.93	0.4-3.6
TG ng/ml	9	2	26	20	2-38
TPO/TG Ab	<0.4/ <0.4	<0.4/ <0.4	<0.4/ <0.4	<0.4/ <0.4	<0.4/<0.4

THRB gene sequencing

Synonymous variant in exon 10
T->C, TTT->TTC (F417F) MAF 0.01
SNP ID **rs13081063**



Intronic variant in intron 9
G->A, MAF 0.05% (2/4298)
SNP ID **rs763751238**

No pathogenic mutation in *THRB* exon 7-10, THRB2 exon1
No mutation in *SBP2, albumin DIO2 and DIO3*

Next Step?

Genes Sequenced

GENES	REASON
THRB 2	Isolated pituitary insensitivity
Albumin, SBP2, DIO3 and DIO3	High rT3 relative to T3

NEGATIVE

PAX8	Determine the cause of CH

POSITIVE: missenese mutation K135R in the *PAX8* gene

Return to CASE 1

WES failed to identify a mutation compatible with athyreosis

PAX8 mutations (Dominant inheritance)

First report:

Macchia PE, et al. Nature Genetics 19:83, 1998

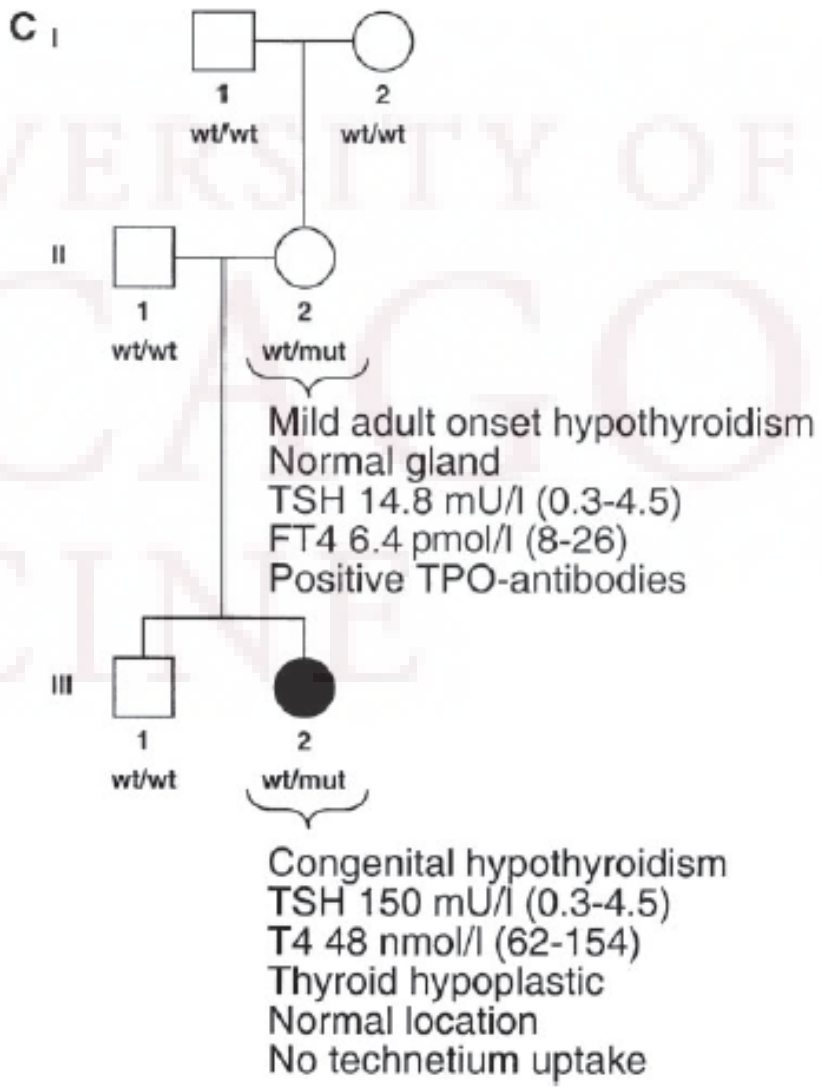
Two sporadic cases on familial (mother and two children)

Phenotypes: CH due to ectopy, hypoplasia, cystic thyroid rudiment

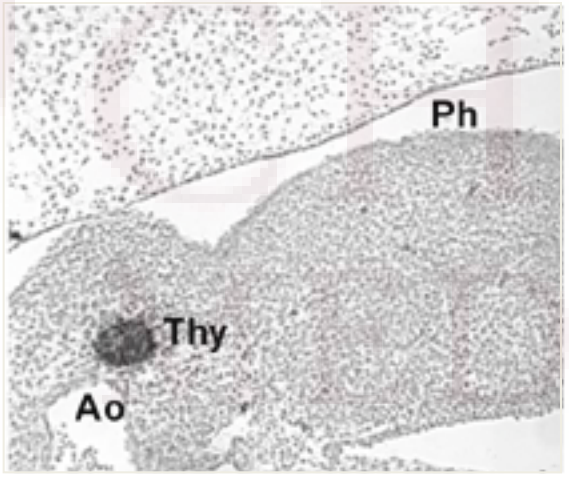
Congdon T, et al. JCEM 86:3962, 2001

Hypo(mother and two children)

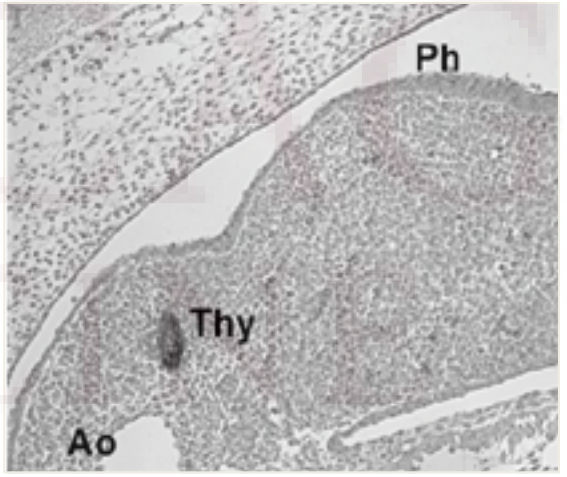
Phenotypes: CH hypoplastic; mild adult hypothyroidism



Pax8 and TTF1 are required for survival and/or proliferation of thyroid precursors



wt embryo



Pax8 $^{-/-}$

Publications of RTHß **R320L**

1. Adams M, Matthews C, Collingwood TN, Tone Y, Beck-Peccoz P, Chatterjee KK. Genetic analysis of 29 kindreds with generalized and pituitary resistance to thyroid hormone: identification of thirteen novel mutations in the thyroid hormone receptor ß gene. J Clin Invest 1994; 94:506-515

2. Erichsen KE, Berg JP, Torjesen PA, Haug E, Johannesen O. Thyroid hormone resistance: clinical, biochemical and genetic study of a family. Tidsskr Nor Laegeforen 1998; 118:525-529

3. Rösler A, Litvin Y, Hage C, Gross J, Cerasi E. Familial hyperthyroidism due to inappropriate thyrotropin secretion successfully treated with triiodothyronine. J Clin Endocrinol Metab 1982; 54:76-82

4 Gross DJ, Larsen PR, Chin WW. Persomal communication. 1998;

5. Mok SF, Loh TP, Venkatesh B, Deepak DS. Elevated free thyroxine and non-suppressed thyrotropin. BMJ Case Rep 2013; 2013

FT4 in affected adults ranged from 170 to 200% (ULN and FT3 165 to 195% ULN with TSH values 3.6 to 26 mU/L. T