The IGSF1 Deficiency Syndrome: An Unusual Case

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Introduction

Background: (IGSF1) deficiency was recently found to be a novel cause of X-linked central hypothyroidism, macroorchidism, and delayed puberty.

Case Presentation: We present a family, in which the **proband** was diagnosed with congenital central hypothyroidism by neonatal screening and treated accordingly. Further pituitary examination revealed an **unmeasurable prolactin level**, normal IGF-1, normal cortisol and no abnormalities of the pituitary on MRI. The patient exhibited normal growth and bone age. However, the patient had **excessive weight gain** and remarkable **testicular enlargement (5-6cc). The enlargement was noticed first at 3.6 years of age** and the macroorchidism was present at least until his last evaluation at age 12 years. At 6.3 years old, the patient still was still prepubertal at LHRH stimulation testing. A pubertal response to LHRH was first observed at 10.3 years old, when his testicular size was 10-12 cc. The proband's brother was referred for short stature at age 13 years and he was found to have central hypothyroidism with a normal prolactin, normal GH secretion and low testosterone level for a testicular size of 25-28 cc (disharmonious pubertal development). His BMI was normal and besides poor growth, he did not have any manifestations of long standing, untreated hypothyroidism. The family was referred **for genetics evaluation**, which revealed that the index patient, his brother, mother and maternal grandfather carry **a nonsense mutation in the *IGSF1* gene, specifically c.3411_3412del.pTyr1137*.** The main clinical characteristics of the IGSF1 deficiency syndrome are congenital hypothyroidism of central origin and macroorchidism. In a variable proportion of affected males, other features are observed, including prolactin deficiency (69%), partial and transient GH deficiency (22%), disharmonious pubertal development (normal timing of testicular growth but delayed rise of testosterone), and increased body mass index (BMI) (1).

#300888

HYPOTHYROIDISM, CENTRAL, AND TESTICULAR ENLARGEMENT; CHTE

CATEGORY	SUBCATEGORY	FEATURES
Inheritance	-	X-linked recessive
Growth	Height	Delayed growth spurt in puberty
		Average height in adulthood
	Weight	Overweight
Genitourinary	External Genitalia (Male)	Normal testicular volume in childhood
		Enlarged testicles in adulthood ?
Endocrine Features	-	Hypothyroidism, central
		Decreased growth hormone (in some patients)
		Decreased serum prolactin
		Delayed testosterone increase at puberty
		Normal testosterone levels in adulthood
Miscellaneous	-	Intrafamilial variability in severity or hypothyroidism
Molecular Basis	-	Caused by mutation in the immunoglobulin superfamily, member 1 gene (IGSF1, 300137.0001)

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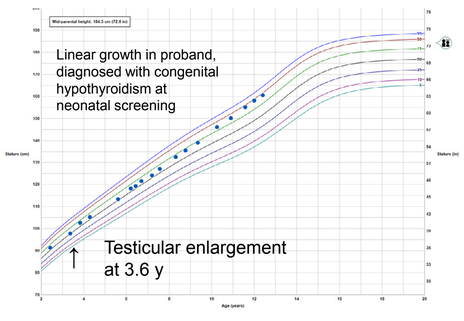
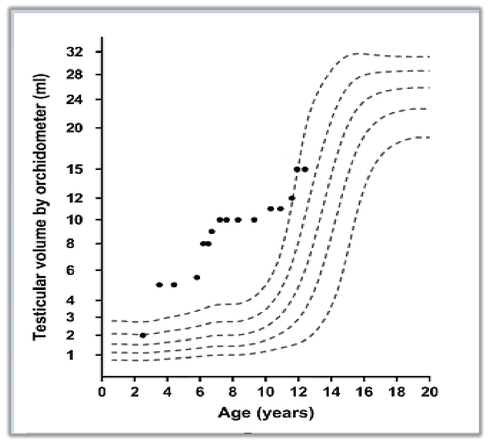


Proband Labs

(blue columns on tx)

Date/Age	DOL 2	DOL 17	DOL 25	DOL 47	DOL 53	DOL 72	11 mo	3.4 y	6 y 3.5 m	9 y 11.5 m
Treatment					Started Lthyroxine 50 mcg daily	↓ dose to 25 mcg daily	Cont 25 mcg daily	Off tx (mom d/c'd at 3 y)	75 mcg daily	75 mcg daily
NB screen result	clotted	Low T4, nl TSH (filter, not serum)								
T4, total mcg/l			4.1 ↓(4.5-12)			19.3↑	7.4	4.9↓	8.1	
Free T4 ng/dL				0.8		11.7↑		0.78		
TSH mIU/L			1.75	3.2		0.02↓	0.46	1.4	<0.01	<0.01
TBG mg/dl				wnl				2.8		
Prolactin ng/mL	Diagnosed with Congenital Hypothyroidism					1.2				<1
Testosterone ng/dL						404↑		<4		<7
IGF-1 ng/mL						50				
Testicular size				2 cc				5-6 cc ? pubertal		10-12 cc ↑
Bone Age	Read as within normal limits		BA 6 y CA 6 y 1 m		BA 7 y – 8 y CA 7 y 6 m					
Thyroid Ultrasound	May 30, 2015 (12 y 5 mo) : **NORMAL**									
Misc. lab Fragile X	Combined Pituitary Hormone Deficiency Evaluation done at Athena : **NORMAL** :Normal									

Proband's Testicular size by orchidometer at different ages



Testicular size, Testosterone level and Pubic hair

Age years	Testicular size cc	Testosterone level	PH , Tanner stage
		Low testosterone level for testicular size (4)	
2.5 years	2cc		
3.5 years	5 cc	<3ng/dl	I
4.4 years	5 cc		
5.8 years	5.5 cc	<20ng/dl	
6.2 years	8 cc		
6.5 years	8 cc	<3ng/dl	
6.7 years	9 cc		
7.2 years	10 cc	<20ng/dl	
7.6 years	10cc		
8.3 years	10 cc	<3ng/dl	II
9.3 years	10 cc		
10.3 years	11 cc		
10.9 years	11cc	<7ng/dl	
11.6 years	12 cc	14 ng/dl	III
11.9 years	15 cc		
12.4 years	15 cc	5 ng/dl	

Work up for Precocious Puberty

Choose Stim Test — Stim Test Date: 3/6/09

test type: Lupron@6 years and 4 mont — samples: 6

			0	60	120	180			
Cortisol, Serum (If Labcorp ,	Norm	3/6/09	9.5						mcg/dl
Testosterone, Total (If Labc	Norm	3/6/09	<3.0						ng/dl
IGF-1 (If Labcorp #500485,	Norm	3/6/09	208						ng/mL
IGFBP-3 (If Labcorp, #5006	Norm	3/6/09	2.2						ug/mL
T4 (If Labcorp, use ES#500:	Norm	3/6/09	8.1						ug/dl
TSH, 3rd generation (If Labc	Low	3/6/09	<0.01						UIU/mL
FreeT 4 (includes T4)(If Labc	Norm	3/6/09	8.1						ng/dL
ACTH -ICMA (If Labcorp, us	Norm	3/6/09	17						pg/ml
Prolactin ,Serum(ICMA)(If La	Low	3/6/09	0.7			1.2			ng/ml
FSH(If Labcorp #500097)	Norm	3/6/09	3/6/2009	0.95	5.5	12	16		miu/ml
LH -ICMA (If Labcorp, use #!	Norm	3/6/09	3/6/2009	0.09	1.9	2.6	3		miu/ml

All Normal | Date Drawn

- **Pituitary MRI normal**

Choose Stim Test — Stim Test Date: 11/2/12

test type: ACTH /Leuprolide@10 y old — samples: 6

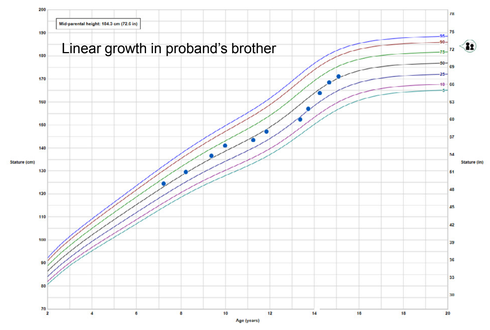
				0	30	60	90	120	180	
Cortisol, Serum (If Labcorp ,	Norm	11/2/12	11/2/2012	10	21	22	24			mcg/dl
Testosterone, Total (If Labc	Norm	11/2/12	11/2/2012	<7.0						ng/dl
IGF-1 (If Labcorp #500485,	Norm	11/2/12	11/2/2012	273						ng/mL
IGFBP-3 (If Labcorp, #5006	Norm	11/2/12	11/2/2012	5.4						ug/mL
FSH(If Labcorp #500097)	High	11/2/12	11/2/2012	2.0		7.1		14.1	17.9	miu/ml
LH -ICMA (If Labcorp, use #!	High	11/2/12	11/2/2012	0.3		3.1		7.0	4.5	miu/ml
Prolactin ,Serum(ICMA)(If La	Low	11/2/12	11/2/2012	<1						ng/ml
ACTH -ICMA (If Labcorp, us	Norm	11/2/12	11/2/2012	32						pg/ml
LH (24hrs after lupron)(If La	Norm	11/2/12	11/2/2012	1.5						
FSH (24hrs after lupron)(If	Norm	11/2/12	11/2/2012	6.0						
DHEA-S (If Labcorp , #5001	High	11/2/12		56.0						mcg/dl

All Normal | Date Drawn

Normal puberty at age 10 years

Brother

The proband's brother was referred for short stature at age 13 years and he was found to have central hypothyroidism with normal prolactin, normal GH secretion and low testosterone level for a testicular size of 25-28 cc (disharmonious pubertal development).



Brother's Labs at diagnosis

Choose Stim Test — Stim Test Date: 4/23/14

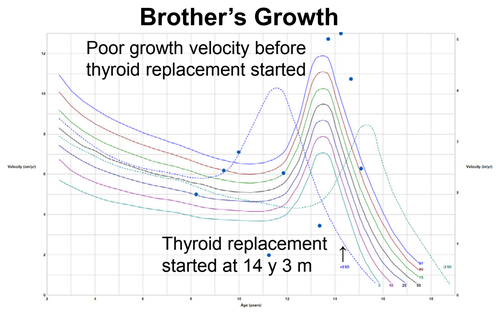
test type: Gh /Lupron /ACTH @15.4 y — samples: 6

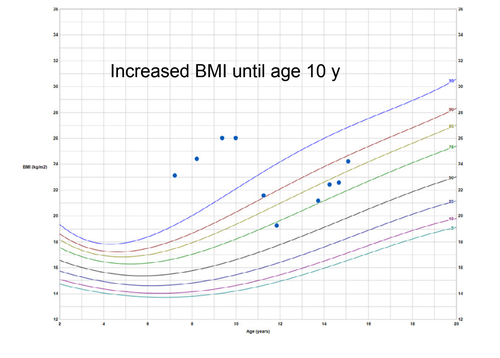
				0	30	60	90	120	180	
Cortisol, Serum (If Labcorp ,	Norm	4/23/14	4/23/2014	7.5	15	21	24	25		mcg/dl
GH (random) (If labcorp, #5(	Low	4/23/14	4/23/2014	0.547	0.943	12	8.2	4.6	3.6	ng/ml
IGF-1 (If Labcorp #500485,	Norm	4/23/14	4/23/2014	453						ng/mL
IGFBP-3 (If Labcorp, #5006	Norm	4/23/14	4/23/2014	3.1						ug/mL
Prolactin ,Serum(ICMA)(If La	Norm	4/23/14	4/23/2014	12					4.8	ng/ml
ACTH -ICMA (If Labcorp, us	Norm	4/23/14	4/23/2014	17						pg/ml
GH Binding Protein (If Labc	Norm	4/23/14	4/23/2014	1499						pmol/L
Testosterone, Total (If Labc	High	4/23/14		460						ng/dl
FSH(If Labcorp #500097)	High	4/23/14		9.9		16		21	30	miu/ml
LH -ICMA (If Labcorp, use #!	High	4/23/14		2.1		17		21	23	miu/ml
TSH, 3rd generation (If Labc	Norm	4/23/14		2.3						UIU/mL

All Normal | Date Drawn

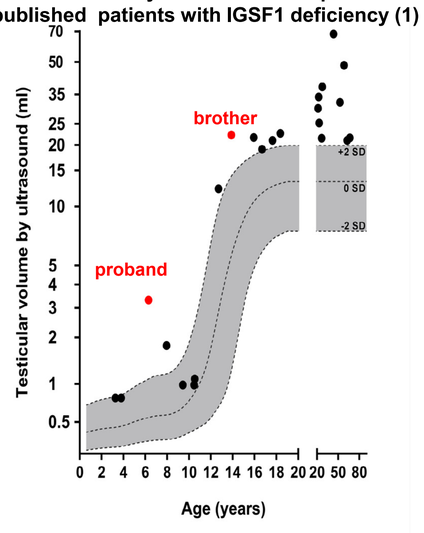
Date/Age	DOL 2	DOL 30	10 y	13.72 y (First visit)	14 y1	14 y 3 m
Treatment			Started ADD tx			Started l-thyroxine 62.5 mcg daily
NB screen	Low T4, nl TSH (filter)	T4 nl (>6) (filter, not serum)		(0.9-1.4)		
Free T4 ng/dL				0.7		
TSH mIU/L				1.54		
Testosterone ng/dL				73	966	
Bone Age				13 y CA 13 y 10 m		
Testicular size				25 cc bilaterally		

Brother's Growth





Testicular size by ultrasound compared to published patients with IGSF1 deficiency (1)



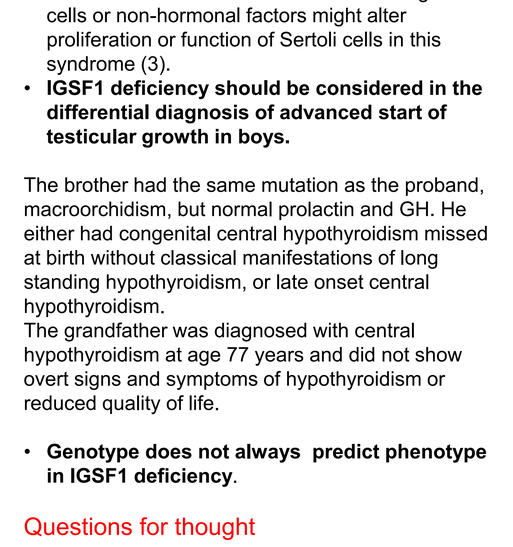
Mother's Labs

Test	Result	Normal range
Free T4	0.9 ng/dL	0.8-1.8
Total T4	6.1 mcg/dL	4.5-12
Total T3	102 ng/mL	76-181
Free T3	3 pg/mL	2.3-4.2
TBG	17 mcg/mL	13.5-30.9
Reverse T3	10 ng/dL	8-25
Prolactin	10.8	3-18.6

Maternal Grandfather's Labs

Test	Result	Normal range
Free T4	0.54 ng/dL (low)	0.76-1.46
Total T4	3.9 mcg/dL (low)	4.5-12.1
TSH	1.610 uIU/mL	0.368-3.740

Central Hypothyroidism



Conclusion

We present here a unique case of a family with IGSF1 deficiency.

- **Testicular enlargement is reported to occur at normal age in these patients (1), but our proband patient had testicular enlargement starting at 3.6 y, making it an unusual case.**
- With respect to macroorchidism, we are assuming an association with hypothyroidism, because Sertoli cell number –which determines testicular size– is influenced by low T3 levels.
- In addition, relatively increased FSH or impaired communication between Sertoli cells and germ cells or non-hormonal factors might alter proliferation or function of Sertoli cells in this syndrome (3).
- **IGSF1 deficiency should be considered in the differential diagnosis of advanced start of testicular growth in boys.**

The brother had the same mutation as the proband, macroorchidism, but normal prolactin and GH. He either had congenital central hypothyroidism missed at birth without classical manifestations of long standing hypothyroidism, or late onset central hypothyroidism.
The grandfather was diagnosed with central hypothyroidism at age 77 years and did not show overt signs and symptoms of hypothyroidism or reduced quality of life.

- **Genotype does not always predict phenotype in IGSF1 deficiency**.

Questions for thought

- Asymptomatic patients; to treat or not to treat?
- Testicular enlargement in our patient happened after family misinterpreted instructions and discontinued thyroid replacement at age 3 years: Coincidence or related?
- Did the brother have "congenital" hypothyroidism that was missed versus late onset?

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Pituitary

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