LEIDEN UNIVERSITY MEDICAL CENTER

IGSF1 deficiency

Clinical and laboratory features in males and females

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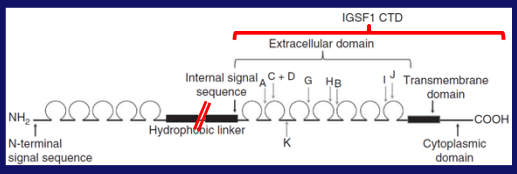
December 11th 2013

On behalf of the IGSF1 consortium

*Immunoglobulin Superfamily member 1 (**IGSF1**)*

- 11 families male central hypothyroidism (NL, UK, Italy)



- Xq25
- Membrane glycoprotein, expressed in pituitary gland and testis

- Mutations impair trafficking to cell membrane
- IGSF1$^{\Delta ex1}$ mice show central hypothyroidism

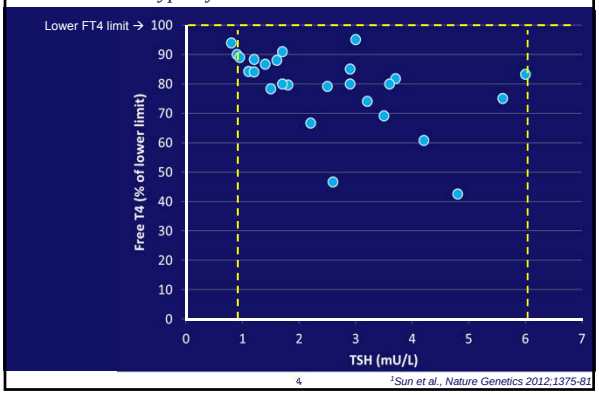
Sun et al., Nature Genetics 2012;1375-81

IGSF1 deficiency - characteristics in males

- 24 male patients (age 0 – 87 years)
  - 17 index cases
    - 12 neonatal screening (Netherlands, Italy)
    - 5 symptoms in infancy/childhood
  - 7 family studies

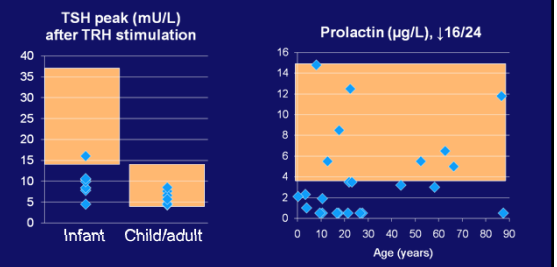
- Endocrine status
- Growth and puberty
- Metabolic status

Central hypothyroidism[1]



4 [1]Sun et al., Nature Genetics 2012;1375-81

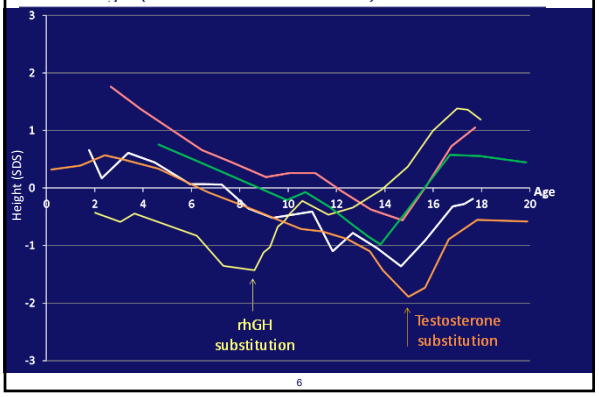
Central hypothyroidism[1]



- LT4 suppletion: 17/17 index, 3/7 non-index
- 3 partial GH deficiency (transient in 2)
- Normal LH and FSH

5 [1]Sun et al., Nature Genetics 2012;1375-81

Height (standard deviation scores)



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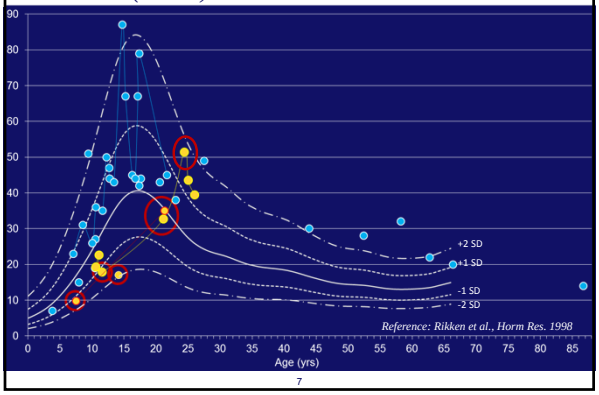
IGF-I (nmol/L)

Chemoluminescentie assay (Immulite 2000; Siemens).



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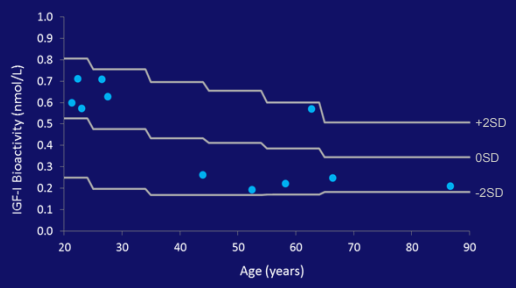
IGF-I bioactivity (nmol/L)

Average IGF-I bioactivity per nmol IGF-I: 1.5±0.6%



IGF-1 receptor Kinase receptor activation assay (KIRA) of 10-fold diluted serum samples[1,2]

1. Chen et al., Am J Physiol Endocrinol Metab. 2003. 2. Brugts et al., J Clin Endocrinol Metab. 2008

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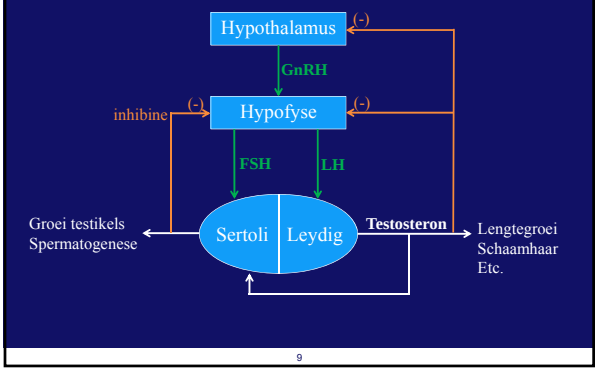
Normal puberty



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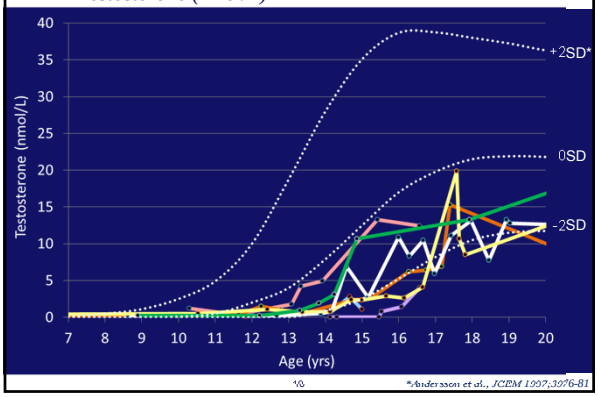
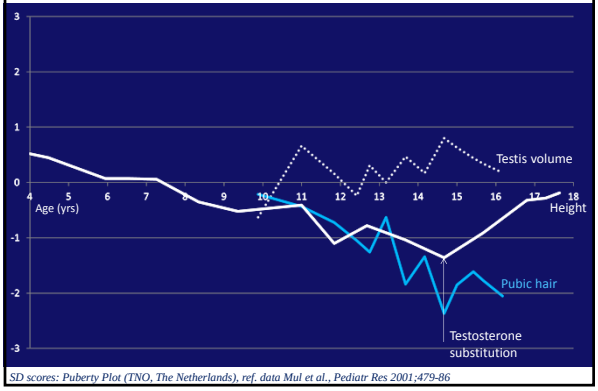
Testosterone (nmol/L)



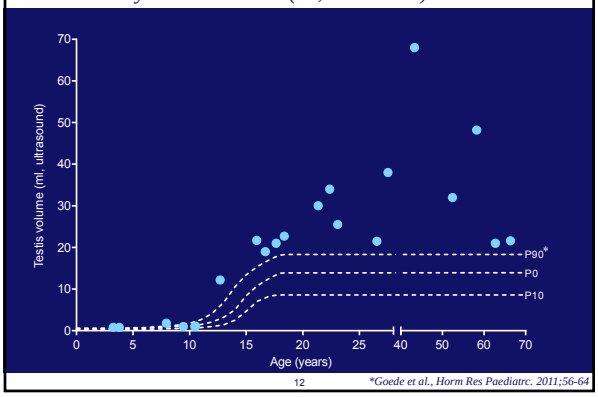
*Andersson et al., JCEM 1997;3376-81

Puberty – Height, Pubic Hair, Testis volume in SDS*



SD scores: Puberty Plot (TNO, The Netherlands), ref. data Mul et al., Pediatr Res 2001;479-86

Puberty – Testis volume (ml, ultrasound)



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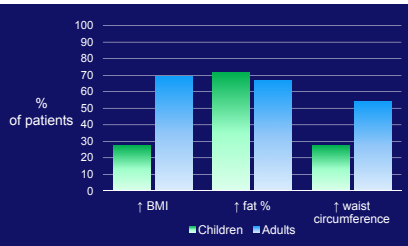
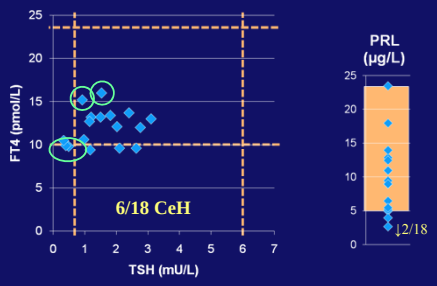
*Goede et al., Horm Res Paediatrc. 2011;56-64

Metabolic status (n=24)



Metabolic syndrome 4/24
(4/5 >55yr, all untreated with LT4)

Females carriers (n=18, age 32-80 yrs)



Skewed X-chromosome inactivation in 4 of 11 females

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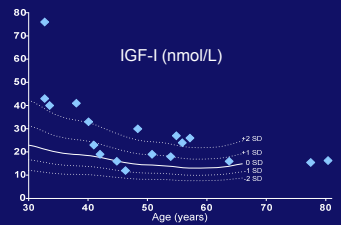
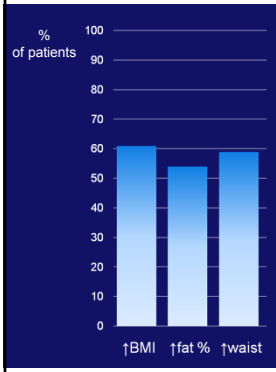
Growth and puberty – female carriers

- Normal growth
- Median age at menarche 14 yrs, range 11-19 yr (≥15 yr in 5)
- Oophorectomy for ovarian cysts in 4/18
- IGF-1 (above) upper half reference range



Metabolic status – female carriers



Metabolic syndrome 3 / 18
- 48 yr (untreated)
- 54 yr (LT4 treated 12 yrs)
- 80 yr (untreated)

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Conclusions – IGSF1 deficiency syndrome

IGSF1 mutations cause a novel, X-linked syndrome

Males

All: Central hypothyroidism, macroorchidism, delayed puberty

Some: Prolactin deficiency, transient GHD, obesity

Females

Central hypothyroidism in 6/18, prolactin deficiency in 2/18, obesity

- *IGSF1* testing in central hypothyroidism or macroorchidism
- If positive → family studies

(hypothyroidism associated with adverse cardiovascular profile[1])

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[1]Doin et al., Eur J Endocrinol 2012;631-40

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