

Introduction

X-linked IGSF1 deficiency syndrome

Males:

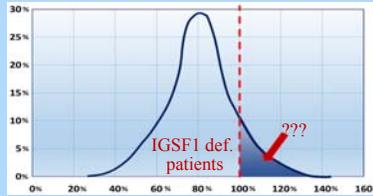
- Central hypothyroidism (CeH)
- Delayed puberty (but normal testis growth)
- Macroorchidism (adults)
- Variable PRL/GH-def or ↑BMI/fat%

Proportion of heterozygous females:

- Mild CeH or PRL-def
- Menarche ≥15 yr
- ↑BMI/fat%

Observation

- CeH was always presenting symptom
- FT4 often only *slightly* decreased (**figure**)
- Likely there are index pts without CeH



FT4 in IGSF1 def. patients, CeH presenting symptom (% of lower limit ref. range FT4)

Question

Can *IGSF1* cause constitutional delay in growth and puberty (CDGP) in the absence of central hypothyroidism?

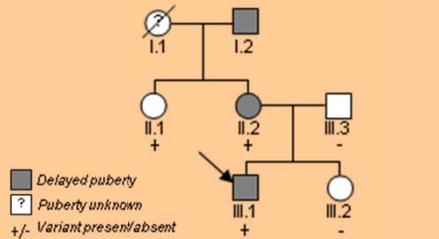
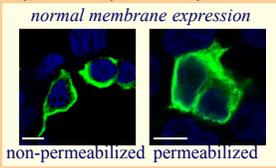
Plan

- Finnish males with familial constitutional delay in growth and puberty: n=268
- Apparent X-linked inheritance: n=30
- Study *IGSF1* *in silico*, *in vitro*, *in vivo*

Results

c.3243G>C, p.Met108Ile

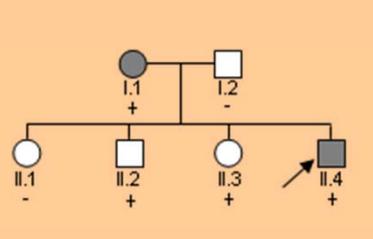
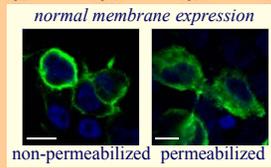
Frequency: 0.1% (Finnish: 0.0%)*



Carrier →	III.1 (M)	II.1 (F)	II.2 (F)
Puberty	Delayed	=	Delayed
Free T4**	Normal	15.4	-
IGF-1	-	=	-
PRL	-	=	-
BMI	=	=	=
Testis size	-	-	-

c.1811A>C, p.Asn604Thr

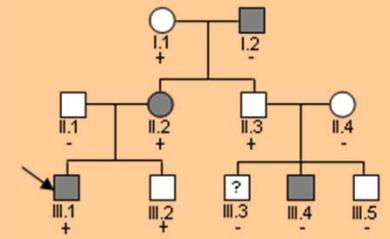
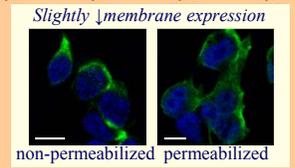
Frequency: 0.7% (Finnish: 2.6%)*



	II.4 (M)	I.1 (F)	II.2 (M)	II.3 (F)
Puberty	Delayed	Delayed	Normal	Normal
Free T4**	13.0	Pr.hypo	14.0	Pr.hypo
IGF-1	=	=	=	=
PRL	↑	↑	=	↑
BMI	↑	↑↑	=	↑↑
Testis size	=	-	=	-

c.2954T>C, p.Val985Ala

Frequency: 0.3% (2.6%)



	III.1 (M)	I.1 (F)	II.2 (F)	II.3 (M)	III.2 (M)
Puberty	Delayed	Normal	Delayed	Normal	Normal
Free T4**	14.0	12.0	15.0	14.0	13.0
IGF-1	=	=	=	~↑	=
PRL	=	=	=	=	=
BMI	=	=	=	↑	=
Testis size	-	-	-	-	=

Discussion

- Variants show normal plasma membrane expression **Does not rule out functional defect**
- Incomplete geno-pheno cosegregation, no other signs of *IGSF1* deficiency in carriers **Known phenotypic variation within families (especially females) → variable penetrance? CDGP in non-carriers of different etiology than index?**
- Small sample size, prevalence 0% → 95% confidence interval 0.0% - 11.4%

Conclusion

IGSF1 mutations are unlikely to be a prevalent cause of CDGP.

