

IGSF1 variants in boys with familial delayed puberty

S.D. Joustra^{1,2}, Karoliina Wehkalampi³, Wilma Oostdijk¹, Nienke R. Biermasz², Sasha Howard⁴, Tanya Silander⁵, Daniel J. Bernard⁵, Jan M. Wit², Leo Dunkel⁴, Monique Losekoot⁶

¹Department of Peditatrics, ²Endocrinology and Metabolism, and ⁶Clinical Genetics, Leiden University Medical Center, Leiden, The Netherlands, ³Children's Hospital, Helsinki University Central Hospital, Helsinki, Finland. ⁴Centre for Endocrinology, Queen Mary University of London, London, United Kingdom. ⁵Department of Pharmacology and Therapeutics, McGill University, Montréal, Canada. Correspondence: sdjoustra@lumc.nl

Introduction

X-linked IGSF1 deficiency syndrome

Males:

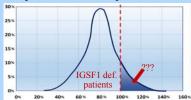
- Central hypothyroidism (CeH)
- Delayed puberty (but normal testis growth)
- Macroorchidism (adults)
- Variable PRL/GH-def or ↑BMI/fat%

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?

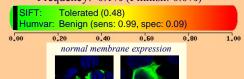
Plan

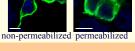
- Finnish males with familial constitutional delay in growth and puberty: n=268
- Apparent X-linked inheritance: n=30
- Study IGSF1 in silico, in vitro, in vivo

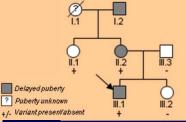
Results

c.3243G>C, p.Met1081Ile

Frequency: 0.1% (Finnish: 0.0%)*







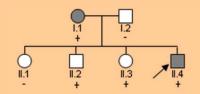
Carrier →	III.1 (M)	II.1 (F)	II.2 (F)
Puberty	Delayed	=	Delayed
Free T4**	Normal	15.4	-
IGF-1	-	=	-
PRL	-	=	-
BMI	=	=	=
Testis size	-	_	-

c.1811A>C, p.Asn604Thr

Frequency: 0.7% (Finnish: 2.6%)*



non-permeabilized permeabilized



II.4 (M)	I.1 (F)	II.2 (M)	II.3 (F)
Delayed	Delayed	Normal	Normal
13.0	Pr.hypo	14.0	Pr.hypo
=	=	=	=
1	1	=	1
1	11	=	1 1
=	-	=	-

IGSF1 mutations are unlikely to be

a prevalent cause of CDGP.

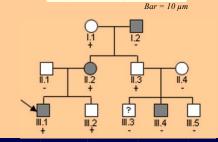
Conclusion

c.2954T>C, p.Val985Ala

Frequency: 0.3% (2.6%)



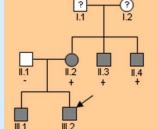
non-permeabilized permeabilized



III.1 (M)	I.1 (F)	II.2 (F)	II.3 (M)	III.2 (M)
Delayed	Normal	Delayed	Normal	Normal
14.0	12.0	15.0	14.0	13.0
=	=	=	~1	=
=	=	=	=	=
=	=	=	1	=
-	-	-	-	=

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 $0\% \rightarrow 95\%$ confidence interval 0.0% 11.4%



The third variant was furthermore detected in this family, but no clinical data are available

