IGSF1 variants in boys with familial delayed puberty

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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%

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%

Observation

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

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

Observation

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

Results

c.3243G>C, p.Met1081Ile

Frequency: 0.1% (Finnish: 0.0%)*

SIFT: Tolerated (0.48)
Humvar: Benign (sens: 0.99, spec: 0.09)

SIFT: Deleterious (0.00)
Humvar: Probably damaging (sens: 0.54, spec: 0.94)

Carrier III.1 (M) II.1 (F) II.2 (F) II.4 (M) I.1 (F) II.2 (M) II.3 (F) III.1 (M) I.1 (F) II.2 (F) II.3 (M) III.2 (M)

Puberty Delayed Delayed Delayed Delayed Normal Normal Delayed Normal Normal

Free T4** Normal 15.4 -

IGF-I - - -
PRL - - -
BMI - - -

Testis size - - -

Conclusion

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

Question

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

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c.1811A>C, p.Asn604Thr

Frequency : 0.7% (Finnish: 2.6%)*

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Humvar: Probably damaging (sens: 0.68, spec: 0.90)

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c.2954T>C, p.Val985Ala

Frequency: 0.3% (2.6%)

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