

Introduction

IGSF1 mutations cause X-linked syndrome†

- Central hypothyroidism + variable PRL-def
- Delayed puberty, but normal testicular growth
- Macroorchidism in adults, normal fertility
- Variable GH-def (children) / high IGF-1 in adults
- ↑BMI/fat%

IGSF1‡

- Plasma membrane glycoprotein
- Expressed in human pituitary gland
- Mice/rat: only in thyro-, somato-, and lactotrophs
- Function unknown
- No detailed knowledge on spontaneous pit. functioning

Aim

Study 24h pituitary hormone secretion in IGSF1 deficient males and matched controls

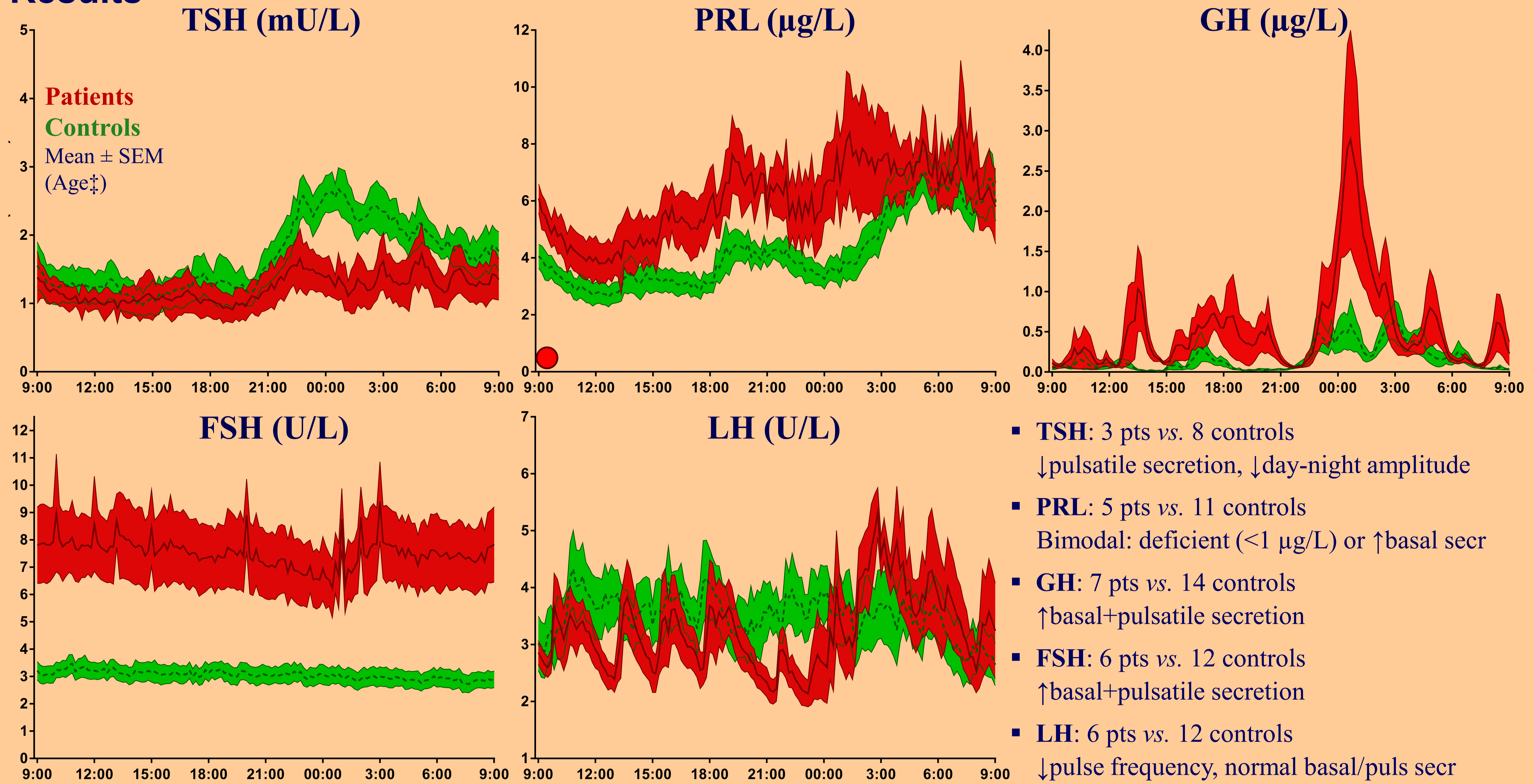
Method

- TSH (if no LT4 Rx), PRL (if basal >1 µg/L), FSH+LH (if no testosterone Rx), and GH (if no rhGH Rx) every 10 minutes for 24 hours
- Deconvolution and modified cosinor for secretion rates and diurnal rhythm (TSH)

Conclusion

- ↓TSH secretion and ↓diurnal variation in TSH
- ↑GH and FSH secretion
- Bimodal distribution of PRL secretion (deficient in some, ↑secretion in others)

Results



Discussion

- ↓Diurnal variation in TSH resembles observations in suprasellar extending pituitary tumours, TRHR mutations, and mice with hypothalamic lesions; thus suggesting ↓TRH signaling at thyrotropes in IGSF1 deficiency. In accordance, *Igsf1* KO mice show ↓pituitary *Trhr* mRNA, and patients show ↓TSH response to exogenous TRH.
- Adult ↑GH (in contrast to occasional GHD in children) concurs with ↓TRH signaling at somatotropes, as TRH stimulates GH in neonatal rats and inhibits it in adult rat and humans (although paradoxical stimulation of GH by TRH has been observed in adults with untreated primary hypothyroidism).
- ↑FSH/↑PRL/=LH is typically seen in untreated primary hypothyroidism, often with delayed puberty but normal timing of testis growth and adult macroorchidism – resembling IGSF1 def. However, IGSF1 def patients show this despite being treated with LT4, and this is the first report in *central* rather than primary hypothyroidism. Alternatively, slowing of GnRH pulse generator or ↓inhibin signaling may cause ↑FSH.

