

Pituitary hormone secretion profiles in the IGSF1 deficiency syndrome*

S.D. Joustra^{1,2}, F. Roelfsema¹, E. Endert³, B.E.P.B. Ballieux⁴, A.S.P. van Trotsenburg⁵, E. Fliers⁶, E.P.M. Corssmit¹, D.J. Bernard⁷, W. Oostdijk², J.M. Wit², A.M. Pereira¹, N.R. Biermasz¹

Departments of ¹Medicine (division of Endocrinology), ²Pediatrics, and ⁴Clinical Chemistry and Laboratory Medicine, Leiden University Medical Center, Leiden, Netherlands. Departments of ³Clinical Chemistry, ⁵Pediatric Endocrinology, and ⁶Endocrinology and Metabolism, Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands ⁷Department of Pharmacology and Therapeutics, McGill University, Montréal, Québec, Canada

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

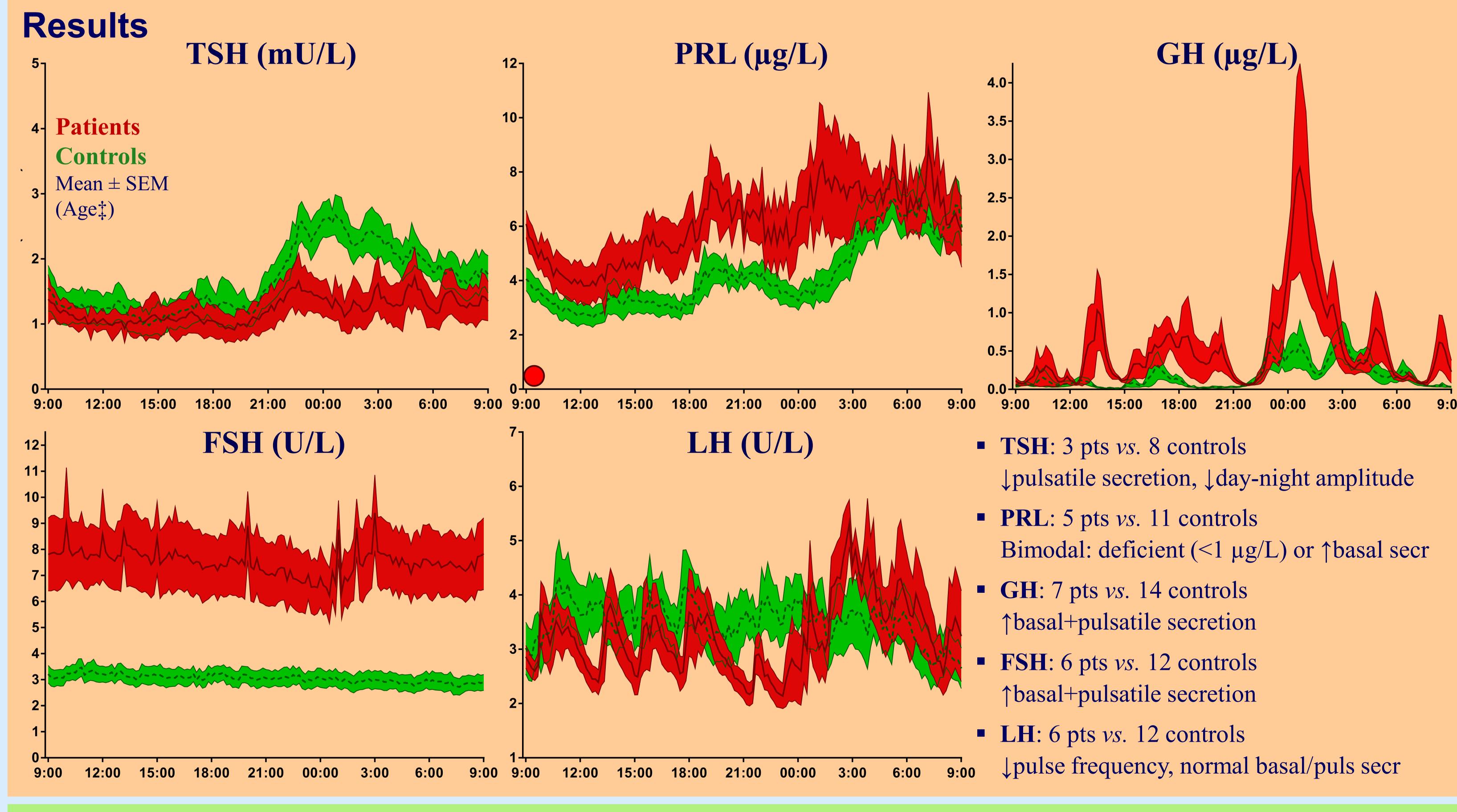
Study 24h pituitary hormone secretion in IGSF1 deficient males and matched controls

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)



Discussion

- Diurnal variation in TSH resembles observations in suprasellar extending pituitary tumours, TRHR mutations, and mice with hypothalamic lesions; thus suggesting JTRH signaling at thyrotropes in IGSF1 deficiency. In accordance, Igsf1 KO mice show Jpituitary 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).
- \tag{FSH/\tag{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 \f\SH.



et al., Neuroendocrinology 2015; in press

† Sun et al., Nat. Genet. 2012; 44(12):1375-81 Joustra et al., JCEM 2013; 98(12):4942-4952 ‡Age median (range): TSH patients 62 yr (53-66 yr), controls 38 yr (33-65 yr); PRL patients 24 yr (18-62 yr), controls 33.5 yr (21-55 yr); LH+FSH patients 26 yr (22-62 yr), controls 44 yr (26-72 yr); GH patients 24 yr (22-63 yr), controls 35 yr (21-64 yr). All *P*>0.05.



