Title: *PROP1*-Related Combined Pituitary Hormone Deficiency *GeneReview* – *POU1F1* Variants

Author: de Graaff L

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Specific variants in *POU1F1*

Many *POU1F1* variants have been described to date. For a comprehensive review, see Pfäffle & Klammt [2011].

Recently, several new *POU1F1* mutations were described:

- In 2011, Tenenbaum et al reported the follow up of a patient with a nonsense mutation, in whom central hypothyroidism was diagnosed at the age of 2 months and GH and PRL deficiencies were documented at 9 months. MRI at 14 years revealed a hypoplastic adenohypophysis. The patient underwent spontaneous but delayed puberty. A novel disease-causing mutation (c.502insT) was identified in the homozygous state in exon 4 of *POU1F1*. This insertion results in a frameshift introducing an early termination codon at position 174 (p.Thr168IlefsX7), leading to a severely truncated protein lacking the entire homeodomain. This mutation abolishes POU1F1's transactivation properties on three target promoters [Tenenbaum-Rakover et al 2011].
- In 2012, Turton et al described a male patient with extreme short stature, learning difficulties, anterior pituitary hypoplasia, secondary hypothyroidism and undetectable prolactin, growth hormone (GH) and insulin-like growth factor 1 (IGF1), with normal random cortisol. In this patient, combined pituitary hormone deficiency in this patient was caused by loss of POU1F1 function by two novel mechanisms, namely aberrant splicing (IVS1+3nt (A>G) and protein instability (R265W).
- Inoue et al 2012 described a novel heterozygous splice site mutation (Ex2 + 1G>T; c.214 + 1G>T) in identical twin brothers with mild CPHD. In vitro splicing studies suggested this mutation to result in an in-frame skipping of exon 2, thus producing an internally deleted protein lacking most of the R2 transactivation subdomain (TAD-R2). Heterologous expression studies of the mutated POU1F1 protein showed modest reductions in its transactivation activities in HEK293T cells, while acting as a dominant-negative inhibitor of the endogenous activities of POU1F1 in pituitary GH3 cells.

References

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