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-Rakov 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


Turton JP, Strom M, Langham S, Dattani MT, Le Tissier P. Two novel mutations in the POU1F1 gene generate null alleles through different mechanisms leading to combined pituitary hormone deficiency. (Clin Endocrinol (Oxf). 2012;76:387-93.