Title: *PROP1*-Related Combined Pituitary Hormone Deficiency *GeneReview* – *LHX4* Variants

Author: de Graaff L

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Specific variants in *LHX4*

- In a French family with CPHD, pituitary and cerebellar defects, and abnormalities of the sella turcica, Machinis et al [2001] identified a G-to-C transversion (IVS4, G-C, -1) in four affected members.
- Pfaeffle et al [2008] identified three heterozygous missense *LHX4* variants (p.Arg84Cys, p.Ala210Pro, and p.Leu190Arg) in five persons out of 253 individuals from 245 families with CPHD. In structural models and functional studies the p.Ala210Pro and p.Leu190Arg mutant proteins showed impaired DNA binding and impaired gene activation, causing the protein to be inactive. The p.Arg84Cys mutant protein showed only reduced activity.
- Castinetti et al [2008] found a new variant in the protein sequence of *LHX4* (Thr99fs) in one of 136 individuals with CPHD and malformations of the brain, pituitary stalk, or posterior pituitary gland [Castinetti et al 2008].
- Tajima et al [2007] found a *de novo* heterozygous Pro366-to-Thr (p.Pro366Thr) substitution in a conserved residue in the C terminus in a 16-month-old Japanese girl with severe CPHD, pituitary defects, small sella turcica, and Chiari malformation. The variant was not found in 80 Japanese controls [Tajima et al 2007].
- In 2010, Dateki et al identified a *de novo* heterozygous 522,009-bp deletion involving LHX4 in a patient with CPHD (GH, TSH, PRL, LH, and FSH deficiencies), anterior pituitary hypoplasia, ectopic posterior pituitary, and underdeveloped sella turcica.
- In 2012, Takagi et al identified two novel heterozygous LHX4 mutations, namely c.249-1G>A and p.V75I. The patient harboring the c.249-1G>A mutation exhibited isolated growth hormone deficiency at diagnosis and a gradual loss of ACTH, whereas the patient with the p.V75I mutation exhibited multiple pituitary hormone deficiency. In vitro experiments showed that both LHX4 mutations were associated with an impairment of the transactivation capacities of POU1F1 and αGSU, without any dominant-negative effects.

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