Title: *PROP1*-Related Combined Pituitary Hormone Deficiency *GeneReview* – *LHX3* Variants

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Specific variants in *LHX3*

- Netchine et al [2000] identified homozygosity for two different *LHX3* variants in affected members of two unrelated consanguineous families with rigidity of the cervical spine and CPHD that involved all the anterior pituitary hormones except ACTH: one was a missense variant (p.Tyr116Cys) and one a 23-bp intragenic deletion.
- Bhangoo et al [2006] identified a homozygous 1-bp *LHX3* deletion (g.159delT) in a boy with CPHD and rigid cervical spine.
- Pfaeffle et al [2007] identified the *LHX3* variants p.Glu173Ter, p.Ala210Val, p.Trp224Ter, and a deletion of the entire gene in seven affected individuals from four families in a cohort of 366 persons from 342 families with CPHD. They concluded that *LHX3* variants are a rare cause of CPHD and that they are associated with mild or severe deficiencies of GH, PRL, TSH, and LH/FSH in all cases. They noted that limited neck rotation was not present in three sibs with CPHD who had an *LHX3* nonsense variant.
- Rajab et al [2008] identified a homozygous large intragenic deletion (3088-bp del) and a homozygous nonsense variant (p.Lys50Ter) in four persons from two unrelated consanguineous families with CPHD and neonatal hypoglycemia, short neck with limited rotation, and mild sensorineural hearing loss. Based on the observations that sensorineural hearing loss was found when three of the individuals with pathogenic variants studied by Netchine et al [2000] were reexamined and that ACTH deficiency was present in one of the persons reported by Rajab et al [2008], they proposed that the phenotypic spectrum of *LHX3* variants includes CPHD (with or without ACTH deficiency) with limited neck rotation and mild sensorineural hearing loss.
- Kristrom et al [2009] found a novel, recessive, A-G splice-acceptor site variation in exon 3, resulting in deletion of the homeodomain and the C-terminus. Like the individuals reported by Rajab et al [2008], the individuals reported by Kristrom et al [2009] had CPHD, restricted neck rotation, and a severe hearing defect.
- In 2011, Bonfig et al reported a novel LHX3 mutation (R77X), which is associated with combined pituitary hormone deficiency including ACTH deficiency, short neck, and sensorineural hearing loss.
- In 2012, Bechtold-Dalla Pozza et found a novel homozygous LHX3 mutation (T194R) was detected in two female siblings from related parents. The index

patient had CPHD featuring deficiencies of GH, LH, FSH, PRL, and TSH, with later onset of ACTH deficiency. She also had a hypoplastic anterior pituitary, respiratory distress, hearing impairment, and limited neck rotation. Both patients had neonatal complications. The affected amino acid is conserved in the DNA-binding homeodomain. Computer modeling predicted that the T194R change would alter the homeodomain structure. The T194R protein did not bind tested LHX3 DNA recognition sites and did not activate the α-glycoprotein and PRL target genes.

- In 2012, Sobrier et al described two new LHX3 defects in a patient with syndromic CPHD, severe scoliosis, and normal intelligence. The paternally inherited c.252-3C>G mutation, which disrupts an acceptor splice site, would lead to severely truncated proteins containing a single LIM domain, resembling LIM-only proteins. Coexpression studies revealed the dominant-negative effect of this LIM-only protein over the wild-type LHX3. The maternally inherited p.Cys118Tyr mutation results in partial loss of transcriptional activity and synergy with POU1F1.

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