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Transcriptional Regulation of Pituitary Development: Clinical Implications

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Abstract

Embryonic and foetal development of human anterior pituitary is governed by a cascade of transcription factors. At the early stage, they orchestrate morphogenesis not only of pituitary, but also of eyes, optic nerves, and both facial and cerebral mid-line structures. Later, transcriptional factors regulate the differentiation of pluripotent pituitary cells into five specific cell lineages of the anterior pituitary-corticotrophs, gonadotrophs, thyrotrophs, somatotrophs, and lactotrophs, allowing the lifelong physiological hormonal production. Therefore, defects in the “early factors” result mostly in dysmorphic syndromes with hypopituitarism, whereas defects in the “late factors” lead to a phenotype of combined pituitary hormone deficiency.

The “sonic hedgehog cascade” (genes SHH, GLI2, PATCH) is expressed already in gestational weeks 3-5, at the stage of morphogenesis of human for brain. Defects in this cascade result in holoprosencephaly, a spectrum of forebrain malformations characterized by failure of the pros encephalon to form two lateral hemispheres. Holoprosencephaly is associated with variable endocrine phenotype. OTX2 gene defects are typically linked to

anophthalmia and hypo pituitarism. Septo-optic dysplasia (mid-line defects, optic nerve hypoplasia and hypopituitarism) may result from HESX1 defects, but also from defects in the FGFR1/FGF8/PROKR2 network, and, rarely, from OTX2, SOX2 or SOX3 mutations. Furthermore, mutations in the “late” transcriptional factors PROP1, POU1F1, LHX3 and LHX4 underlie combined pituitary hormone deficiency (CPHD) without major dysmorphic features, allowing etiological explanation of about 25% cases of “idiopathic” CPHD.

The identification of genetic cause of hypopituitarism in a pediatric patient allows not only genetic counselling in affected family and prenatal diagnosis in most severe defects, but also clinical prediction of risk of hormonal deficiencies (in holoprosencephaly and septo-optic dysplasia) or of evolving hormonal phenotype within the life-span (e.g. ACTH deficiency in PROP1 defect in adolescence or early adulthood). Besides, genetic finding of a PROP1 defect may confirm benign nature of a pituitary mass that may be described as a large pituitary adenoma by a radiologist and might lead to unnecessary neurosurgical intervention.



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