Genetic causes of combined pituitary hormone deficiencies in humans

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Abstract

Congenital hypopituitarism is a rare disease, usually induced by mutations of genes coding for transcription factors involved in pituitary development. PROP1 mutations represent the first cause of identified congenital hypopituitarism. Current techniques only identify 10–20% of congenital hypopituitarism etiologies, suggesting that new techniques are needed to improve this ratio. This should lead to a better management and follow-up of patients presenting with combined pituitary hormone deficiencies.

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Syndromic combined pituitary hormone deficiencies (CPHD) is defined by congenital pituitary deficiencies, associated with extra-pituitary phenotype. Congenital hypopituitarism is usually divided in syndromic (mutations of genes coding for extra-pituitary anomalies, i.e. HESX1, LHX3, LHX4, SOX2, SOX3 or OTX2) and non-syndromic (mutations of genes coding for late acting transcription factors, like PROPI and POU1F1).

Current knowledge on the main phenotypic signs induced by mutations of these genes is briefly summarized below. Our own experience in the GENHYPOPIT network, which is aimed at identifying new etiologies of congenital hypopituitarism will also be concisely reviewed.

Syndromic combined pituitary hormone deficiencies (CPHD) is defined by congenital pituitary deficiencies, associated with extra-pituitary anomalies. These forms of CPHD are induced by mutations of genes coding for early acting transcription factors:
● **HESX1** mutations can be heterozygous or homozygous. Pituitary phenotype is variable, from isolated GH deficiency to panhypopituitarism. Pituitary hypoplasia can be associated with pituitary stalk section and ectopic posterior pituitary. Extra-pituitary anomalies (septo-optic dysplasia, corpus callosum hypoplasia, ...) have also been reported in patients with **HESX1** mutations;

● **LHX3** mutations are homozygous. Pituitary phenotype includes GH, TSH and LH/FSH deficiencies. Corticotroph deficiency is constant. Pituitary hypoplasia can be associated with hearing loss, and cervical spine anomalies, with a rigid neck;

● **LHX4** mutations are heterozygous. Pituitary phenotype includes GH, TSH and ACTH deficiencies. Pituitary hypoplasia can be associated with pituitary stalk interruption. Corpus callosum anomaly has also been reported [2];

● **SOX2** mutations are heterozygous. Pituitary phenotype includes hypogonadotropic hypogonadism that may be associated with GH deficiency. Pituitary hypoplasia can be associated with eye anomalies (anophthalmia, microphthalmia, ...), hearing loss, hypothalamic hamartoma, and learning difficulties;

● **SOX3** mutations are transmitted as an X-linked recessive trait. Isolated growth hormone deficiency is usually associated with mental retardation. Pituitary hypoplasia and ectopic posterior pituitary are often observed;

● **OTX2** mutations are heterozygous. Pituitary hypoplasia can be associated with pituitary stalk interruption and ectopic posterior pituitary. **OTX2** mutations have been initially been reported in ocular anomalies (anophthalmia, microphthalmia) with or without pituitary deficiencies.

Non-syndromic CPHD does not include any extra-pituitary anomaly. They are mainly represented by **POU1F1** and **PROP1** mutations, which are the first that have been reported in the literature about 15–20 years ago:

● **PROP1** mutations are homozygous. Pituitary phenotype always includes somato-lactotroph, thyrotroph and gonadotroph deficiencies. Some patients present delayed onset corticotroph deficiency. Pituitary MRI may show pituitary hypoplasia sometimes preceded by pituitary hyperplasia. **PROP1** mutations represent the most frequently identified genetic etiology of CPHD;

● **POU1F1** mutations are heterozygous or homozygous. Pituitary phenotype includes somato-lactotroph and thyrotroph deficiencies, and pituitary hypoplasia on MRI.

To try and better identify genetic etiologies of isolated or combined congenital hypopituitarism, the GENHYPOPIT network [3] was launched as an international multicentric study about 15 years ago. We collected 989 DNA samples from 649 hypopituitary patients (and 340 unaffected relatives) investigated in 20 countries by more than 220 physicians (469 pedigrees). The present report is focused on transcription factor gene analysis applying a genetic screening strategy based on endocrine and neuroradiological phenotype according to current published knowledge, to establish the prevalence of gene defects in each category of patients and to provide a useful framework for clinicians to determine the genetic etiology and allow genetic counseling for affected individuals and families. In CPHD, tested genes included **POU1F1** (Pit-1), **PROP1**, **LHX3**, **LHX4**, **HESX1**, **OTX2**, and **SOX3**. For each gene, all exons and intron-exon boundaries were analyzed by direct sequencing.

Among the 748 patients (325 females), 172 had isolated deficiency (n = 139 index cases) and 576 had CPHD (from 472 unrelated families). Of the 694 pedigrees, 104 were observed as familial cases, 590 were sporadic, and 65 index cases were born from a consanguineous union. Phenotype included different combinations of hormonal deficiency affecting GH (70.4% of the whole cohort), TSH (55%), LH/FSH (50.4%) or ACTH (50.5%). Several phenotypic associations were recorded like deafness (n = 9) or mental retardation (n = 38). Isolated deficiency included 91 GH (IGHD), 64 ACTH, five TSH, and 12 FSH/LH deficiencies. Pituitary stalk interruption syndrome was found in 20 IGHD patients and 186 with CPHD, and SOD in 13 and 21 cases, respectively. In CPHD, using a phenotype-based algorithm for genotyping (adapted from Reynaud, 2006), 44 pathogenic mutations were identified (13.5%). PROP1 was by far the most frequently identified genetic cause of hypopituitarism with homozygous or double heterozygous mutations found in 38 pedigrees. Among 419 patients tested for PROP1 gene anomalies, 87 were in a familial context (26 mutations, 29.9%), and 332 were sporadic cases (23 mutations, 6.9%).

Typically, patients with **PROP1** mutations present panhypopituitarism (some with maintained ACTH function) and normal location and morphology of the posterior pituitary and pituitary stalk. Pathogenic allelic variations of **POU1F1** (Pit-1) in a homozygous form in patients with GH, prolactin, and TSH deficiencies, **LHX3** (homozygous), **LHX4** (heterozygous), and **HESX1** were found in 1, 1, 2, and 3 distinct pedigrees (two homozygous, one heterozygous), respectively, in patients with variable phenotypic features both between and within families. In vitro transfection studies were performed in many cases to confirm the deleterious functional consequence of these mutations. No mutations were found in **OTX2** and **SOX3**.

To conclude, identifying new etiologies of CPHD should first improve post-natal diagnosis (early treatment of deficiencies, prediction of pubertal outcome, diagnosis of pituitary hyperplasia, and familial genetic diagnosis), and possibly in following years, prenatal diagnosis. Despite our efforts, and the ones from other laboratories involved in pituitary development, only less than 15% of the aetiologies of congenital hypopituitarism have currently been identified. Apart from as yet successful candidate gene approaches, novel high throughput techniques (CGH array, exome sequencing, ...) should allow increasing this relatively low ratio. Other pathophysiological mechanisms, like impaired rhythmicity or auto-immunity, might also be involved, but research on these specific fields is only beginning.
Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References

