

# Genetic causes of combined pituitary hormone deficiency

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**UNIVERSITY OF ZAGREB  
SCHOOL OF MEDICINE**

**Tamara Foro**

**Genetic causes of combined pituitary  
hormone deficiency**

**Graduate thesis**



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## **ABBREVIATIONS**

GH – Growth Hormone

PRL – Prolactin

FSH – Follicle Stimulating Hormone

LH – Luteinizing Hormone

TSH – Thyroid Stimulating Hormone

ACTH – Adrenocorticotrophic Hormone

IGHD – Isolated Growth Hormone Deficiency

CPHD – Combined Pituitary Hormone Deficiency

PSIS – Pituitary Stalk Interruption Syndrome

SOD – Septo-Optic Dysplasia

HPE – Holoprosencephaly

SHH – Sonic Hedgehog Signalling Pathway

HH – Hypogonadotropic Hypogonadism

EPP – Ectopic posterior pituitary

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## **SUMMARY**

Combined pituitary hormone deficiency is a complex disorder requiring life-long follow-up and therapy. Depending on the underlying condition, individuals may be deficient in any number of pituitary hormones and may be at risk for developing further pituitary hormone deficiencies with age. Around 30 genes were implicated in the etiology of this disorder in a variety of syndromic and non-syndromic presentations. Overall incidence of mutations in known genes in patients with CPHD is low, indicating that many genes have yet to be identified. The following text describes clinical, hormonal and imaging phenotype of specific mutations implicated in both syndromic and non-syndromic CPHD.

## **SAŽETAK**

Kombinirani nedostatak hormona hipofize složen je poremećaj koji zahtijeva cjeloživotno praćenje i terapiju. O uzročnom čimbeniku ovisi koji hormoni hipofize nedostaju, a pojedinci s godinama mogu razviti daljnji nedostatak hormona. Oko 30 gena uključeno je u etiologiju ovog poremećaja s različitim sindromskim i nesindromskim prezentacijama. Ukupna incidencija mutacija poznatih gena u bolesnika s ovim poremećajem je niska, što ukazuje na to da mnoge gene tek treba identificirati. Sljedeći tekst opisuje pojedine mutacije povezane sa sindromskim i nesindromskim nedostatkom hormona hipofize te njihove kliničke, hormonalne i MRI prezentacije.



## 1. INTRODUCTION

The pituitary gland is a small endocrine organ located within the sella turcica in the midline of the brain. The gland consists of three lobes – anterior, intermediate and posterior lobe. Anterior and intermediate lobe have different embryonic origin than the posterior lobe and from there stems the division of the pituitary into adenohypophysis and neurohypophysis. The adenohypophysis encompasses the anterior and intermediate lobe and develops from oral ectoderm invagination called Rathke's pouch. Neurohypophysis or the posterior lobe of the pituitary gland develops from neural ectoderm of ventral diencephalon (1).

Anterior lobe is composed of five cell types, each producing specific hormones: somatotrophs – producing growth hormone (GH), lactotrophs - prolactin (PRL), gonadotrophs - follicle stimulating hormone (FSH) and luteinizing hormone (LH), thyrotrophs - thyroid stimulating hormone (TSH) and corticotrophs producing adrenocorticotrophic hormone (ACTH). Intermediate lobe contains melanotrophs producing pro-opiomelanocortin which is the precursor to melanocyte-stimulating hormone and endorphins. Posterior lobe contains axons of neurons whose cell bodies are located in the hypothalamus and are responsible for secretion of antidiuretic hormone and oxytocin.

The pituitary gland plays a critical role in the development and growth by influencing metabolism, puberty, stress response, lactation and reproduction (2) and it does so by responding to signals from the hypothalamus. Hypothalamus coordinates central and peripheral signals to maintain internal balance of the body and sends signals to the pituitary through the hypothalamic-pituitary stalk.

Deficiency of pituitary hormones or hypopituitarism can result either from dysfunction of the pituitary gland itself or from dysfunction of the hypothalamus. Any diseases of the hypothalamus or the hypothalamic-pituitary stalk that result in failure of the normal hypothalamic signals to reach the pituitary can result in hypopituitarism. Hypopituitarism may be limited to a single hormone or multiple hormones may be lacking. In case a single hormone is lacking, the condition is referred to as Isolated Hormone Deficiency. Isolated Growth Hormone Deficiency (IGHD) is the most common type. In case at least two pituitary hormones are deficient, the diagnosis of Combined Pituitary Hormone Deficiency (CPHD) is established (3).

## **2. COMBINED PITUITARY HORMONE DEFICIENCY**

Combined pituitary hormone deficiency may develop due to acquired causes such as trauma, brain surgery, tumor mass effect, infection, radiation exposure, autoimmune diseases, infiltrative diseases or the role may be genetic presenting as congenital hypopituitarism (1). The younger the child is at time of presentation, the more likely the etiology is congenital. However, congenital forms may be diagnosed well after birth (4).

Most commonly, CPHD presents as a combination of GH and one additional pituitary hormone. In the world, the prevalence of CPHD is considered to be 1 in 8000. Although increased number of genetic causes have been identified, around 84% of the patients with CPHD still have no genetic diagnosis even though a familial history of the condition suggests a genetic etiology (2, 5).

### **2.1. Clinical presentation**

Clinical presentation of hypopituitarism considerably varies based on the number and severity of hormone deficiencies. Time of onset of CPHD varies greatly as well and patients may initially be asymptomatic at birth and discovered only when they start to exhibit reduced growth velocity. However, mutation in any of the genes involved in the pituitary development may result in congenital hypopituitarism with immediate presentation at birth.

Growth hormone deficiency is suspected in children with neonatal hypoglycemia and microphallus. Fetal growth is not affected by GH, therefore length and weight at birth are typically normal (2). In childhood, deficiency of GH leads to short stature and growth velocity and if left untreated it can cause disturbed body composition with a reduction in lean body mass and excess fat.

Central hypothyroidism presents due to deficient TSH. When compared with hypothyroidism caused by the damage of the thyroid gland, children with central hypothyroidism typically have higher hormone levels and therefore fewer symptoms (4). Congenital hypothyroidism can have devastating effects on neurocognitive development. Signs and symptoms of congenital hypothyroidism are poor feeding, constipation, hypothermia, bradycardia, prolonged jaundice and poor growth but obvious clinical manifestations of hypothyroidism are usually absent even in newborns with severe hypothyroidism (6).

Gonadotropin deficiency results in low concentrations of sex-specific sex steroids: testosterone in males and estrogen in females. In a male infant with micropenis, with or without cryptorchidism, deficiency of gonadotrophins should be suspected. Children with gonadotropin deficiencies present with failure to start or progress through puberty. In girls, this is seen as inadequate breast development and absence of menarche and in boys as absence of testicle and penis enlargement. Radiological confirmation of lack of pubertal initiation in females by pelvic ultrasound may be helpful if the ovaries and uterus are prepubertal in size. Deficiencies in testosterone/estrogen increase the risk for osteoporosis as well as metabolic abnormalities (7).

Loss of ACTH results in disability of the adrenal gland to secrete cortisol. The clinical presentation can be gradual and nonspecific to hypotension or shock, so-called adrenal crisis, depending on the degree of insufficiency and precipitating stress events. Symptoms include fatigue, nausea, muscle weakness, and headache. Lack of cortisol in the setting of stressful situations such as infection, fever, surgery or trauma is a life threatening situation. Shock can develop due to significant vomiting and dehydration (8).

Neonates with congenital hypopituitarism may present with non-specific symptoms such as hypoglycemia or jaundice and there may as well be associated developmental defects such as ocular, midline or genital anomalies. In the neonatal period, besides hypoglycemia and jaundice, poor weight gain, temperature and hemodynamic instability and recurrent sepsis may occur (3, 4).

Hypoglycemia can present with lethargy and seizures and is the most common and the most important presenting feature of congenital hypopituitarism. It develops due to GH deficiency and is especially prominent in cases where there is associated ACTH deficiency. ACTH controls the production of cortisol and cortisol together with GH protects against hypoglycemia by acting as counter regulatory hormone to insulin. Without GH or cortisol, insulin acts unopposed and since the protective mechanisms of infants are not fully developed, they are at high risk of developing severe and recurrent hypoglycemia which may lead to permanent brain damage (4).

## **2.2. Role of transcription factors in the etiology of CPHD**

Genetics of the pituitary gland is fairly complicated, since the development of the gland is a complex process well influenced by input from adjacent tissues, cellular signalling molecules and transcription factors. Mutations in genes expressed in the developing brain, hypothalamus

or the pituitary can cause CPHD (5). Various genes encode for transcription factors which coordinate the ontogenesis of the pituitary gland, maintain the differentiated state of the developed gland and mediate expression of cell type specific pituitary hormones. Impaired expression or function of these transcription factors cause abnormalities in the development of the gland which can eventually result in diminished or nonexistent secretion of pituitary hormones (2).

Two categories of genes involved in the etiology of CPHD may be identified.

The first group includes genes involved in the early stages of the development of the pituitary gland and are therefore referred to as early-acting genes. These early-acting genes are also expressed in regions that determine formation of the forebrain and midline structures. Patients with mutations in these genes exhibit complex phenotype. Besides anterior pituitary hormone deficiency they present with extra pituitary abnormalities or malformations which can be seen on MRI such as pituitary stalk interruption syndrome (PSIS) or midline defects (2, 9)

The second group of genes is involved in the later stages of the development of the gland and their expression is limited to the developing pituitary. Mutations in these genes produces no extra-pituitary malformations and phenotype of patients with mutations in these transcription factors is described as “pure” endocrine phenotype (9).

List of early and late acting pituitary transcription factors is shown in Table 1.

Mutated transcription factors are always associated with multiple hormone deficiencies. No transcription factor regulates only one hormone expression or guides only one cell development (2). Around 30 genes have been found to cause CPHD until now.

Phenotype of patients with transcription factor mutations can be highly variable. One gene mutation can induce different phenotypes while the same phenotype can be attributed to different transcription factor mutations.

Table 1. Division of pituitary transcription factors into early- acting and late-acting

<b>Early-acting pituitary transcription factors</b>	<b>Late acting pituitary transcription factors</b>
SHH, GLI2	PROP1
HESX1	POU1F1
FGF8 AND FGFR1	
Prokineticin pathway: PROK2 and PROKR2	
OTX2	
SOX2 AND SOX3	

PITX2	
ARNT2	
LHX3 AND LHX4	

### 3. CPHD WITH ASSOCIATED EXTRAPITUITARY ANOMALIES

As previously noted, patients with mutations in genes implicated in the early stages of the development of the pituitary tend to present with hormonal deficits as part of a syndrome with abnormalities in structures such as eye and forebrain. This occurs due to the fact that these structures share common embryological origin with the pituitary gland (3).

#### 3.1. Midline anomalies

Midline anomalies include a wide range of phenotypic signs, from cleft palate and pituitary stalk interruption syndrome to septo-optic dysplasia (SOD) or holoprosencephaly (HPE) (9). The following genes have been associated with these anomalies: SHH, HESX1, SOX2, SOX3, OTX2.

Pituitary stalk interruption syndrome is an antenatal anatomical defect characterized by findings of ectopic location of posterior pituitary together with a thin or absent pituitary stalk and a hypoplastic anterior pituitary gland. PSIS manifestations include a wide spectrum of clinical phenotypes and pituitary hormone deficiencies of variable degree and timing of onset (10). PSIS is a very common feature of CPHD and rarely occurs in IGHD. In case a patient presents with IGHD and PSIS it is important to follow up the patient because they are at an increased risk of progression to CPHD (10, 11).

Septo-optic dysplasia or de Morsier Syndrome occurs due to altered midline craniofacial development and patients with SOD present with at least two of the following: underdeveloped optic nerves, dysfunctional pituitary and brain malformations including septum agenesis or corpus callosum agenesis. Rarely, the eye abnormalities may be more severe including anophthalmia or severe microphthalmia. Neurological manifestations are common and range from focal deficits to global developmental delay (12). Approximately 30% of patients present with a complete triad of symptoms mentioned and 62% of patients with SOD have some degree of hypopituitarism. Hypopituitarism may vary from IGHD to panhypopituitarism – deficiency of all pituitary hormones. Most commonly, GH, TSH and ACTH deficiency are present. Considering the fact that pituitary deficiencies may progress over time, it is important to regularly follow-up these patients. Mutations in early-acting pituitary transcription factors

HESX1, SOX2 and SOX3 have been implicated in the etiology of this disorder but in majority of these patients, genetic mutations have not been identified (3, 12).

When forebrain of the embryo fails to separate into two cerebral hemispheres, HPE occurs. It is a complex brain malformation occurring due to an abnormal division of prosencephalon and may or may not be associated with other craniofacial midline structural abnormalities or eye defects (5). Facial anomalies can present as cyclopia, median or bilateral labial or palatal cleft, hypotelorism, or a single median incisor. Frequently associated with this disorder is mental retardation. In patients with HPE, most common associated endocrinopathy is deficiency of posterior pituitary hormone ADH although anterior pituitary deficiencies occur as well. Mutations in Sonic Hedgehog signaling pathway (SHH) and GLI2 (mediates SHH signals) have been implicated in the etiology of this disorder (3).

According to (5), newer data suggest that CPHD is part of a spectrum disorder with holoprosencephaly and septo-optic dysplasia at the severe end and hypogonadotropic hypogonadism (HH) and IGHD at the mild end of the spectrum. Disruption is probably multifactorial, with environmental as well as genetic influences. This overlap occurs due to common developmental programs of this structure since the developmental regulation of the eye, ear, nose and the pituitary gland together with some cranial nerve ganglia involves common genetic pathways. HH is a disorder characterized by insufficiency of gonadotropins, reduced sex hormone production and infertility or delayed puberty.

### **3.1.1. Sonic-hedgehog (SHH) pathway and GLI2**

GLI transcription factors are targets of Sonic-hedgehog (SHH) signalling pathway in the pituitary gland. Together, they are involved in early steps of the pituitary development. Mutations of SHH and GLI2 have been reported in patients with HPE (6).

SHH is expressed in the ventral diencephalon and plays an important part in midline formation, forebrain development, brain lobe determination and eye formation (12). Clinical phenotype can be highly variable ranging from closely spaced eyes or single maxillary incisor to cyclopia. SHH mutations or variants are a common cause of congenital hypopituitarism in patients with usually complex midline cerebral defects (13).

Besides pituitary hormone deficiency and variable degree of craniofacial abnormalities, patients with GLI2 mutations also present with features such as postaxial polydactyly, single nares, single central incisor and partial agenesis of corpus callosum (3). Arnhold et al. (14)

reviewed the literature for patients with hypopituitarism and alterations in GLI2. Twenty-five patients (16 families) had heterozygous mutations, and the phenotype frequently included GH deficiency, a small anterior pituitary lobe and an ectopic/undescended posterior pituitary lobe on magnetic resonance imaging and postaxial polydactyly. The inheritance pattern was autosomal dominant with incomplete penetrance and variable expressivity. The mutation was frequently inherited from an asymptomatic parent. Furthermore, they concluded that a relatively high frequency of GLI2 mutations and variants were identified in patients with congenital GH deficiency without other brain defects, and most of these patients presented with combined pituitary hormone deficiency and an ectopic posterior pituitary lobe. According to (5), one third of patients with GLI2 variants exhibit CPHD and most of these (83%) are nonsyndromic, meaning that they don't exhibit features of HPE, cleft palate or polydactyly.

### **3.1.2. Hesx1**

Hesx1 is one of the earliest markers of pituitary primordium and it plays a critical role in differentiation of the gland. It is a transcriptional repressor and its down-regulation is required for cellular differentiation and activation of a later-acting genes such as PROP1.

Expression of Hesx1 was found to be restricted to Rathke's pouch. All patients with these mutations exhibit GH deficiency and in majority of cases pituitary hypoplasia can be seen on MRI. In 50% of patients, this mutation is associated with the deficiency of another pituitary hormone. Of the extrapituitary abnormalities, optic nerve anomalies have been observed in 30% of patients. Heterozygous mutations show a milder phenotype and most cases are sporadic. Homozygous mutations were reported in 40% of cases with findings such as optic nerve hypoplasia, hypoplastic corpus callosum and ectopic posterior pituitary. Although optic nerve anomalies are commonly present in patients with these mutations, only 1% of patients with SOD have been linked to HESX1 mutations (9, 15).

### **3.1.3. Fgf8 and Fgfr1**

These transcription factors are responsible for proper Rathke's pouch development and temporo-spatial pattern of pituitary cell lineages. FGF8 (Fibroblast growth factor 8) is a member of the ubiquitously expressed fibroblast growth factor (FGF) family of signalling molecules and its receptors. FGF8 is necessary for proper LHX3 expression (16). Overexpression of FGF8 leads to melanotroph and corticotroph lineage stimulation and inhibition of gonadotroph, somatotroph, thyrotroph and lactotroph lineages. Ear hypoplasia, dental agenesis, cleft palate and distal limb malformations have been reported as well as

septo-optic dysplasia. Most patients with FGF8 mutations have Kallmann syndrome (5) which presents as HH and anosmia. Mutations in FGF8 may cause SOD, HPE or HH/KS.

FGFR1 is a tyrosine kinase receptor belonging to the FGF family. It plays an important role in the development of nervous system, also during Rathke's pouch development. Mutations have been reported for HH with or without anosmia. Mutations in both FGF8 and FGFR1 have been associated with SOD and corpus callosum agenesis. Raivio et al. (17) were first to describe 3 FGFR1 variants in patients with SOD and hypogonadotropic hypogonadism. Two of these patients had GH deficiency and one had panhypopituitarism. Two had corpus callosum agenesis and the third patient had microphthalmia. Another three novel heterozygous variants were reported in four unrelated patients with pituitary hypoplasia and ectopic posterior pituitary and hormone deficiencies ranging from GH and LH/FSH deficiency to panhypopituitarism. These variants had already been reported in patients with isolated hypogonadotropic hypogonadism suggesting incomplete penetrance (16).

#### **3.1.4. Prokinectin pathway: PROK2 and PROKR2**

Prokinectin pathway was reported to be involved in portal angiogenesis and neuronal migration and therefore, is thought to be a possible cause of PSIS, although general prevalence of these mutation in PSIS is estimated to be below 3% (9) Association of PROK2/PROKR2 with HH and Kallmann syndrome and SOD has been reported as well. Patients with wide range of phenotypes from hypogonadotropic hypogonadism associated with SOD, to panhypopituitarism without SOD were reported. Some patients had corpus callosum hypoplasia and optic nerve anomalies. Majority of variants described in these patients were already reported in patients with isolated hypogonadotropic hypogonadism. (16).

### **3.2. Eye anomalies**

#### **3.2.1. OTX2**

OTX2 is a transcription factor involved in the early stages of brain and eye development and as well in development of GnRH neurons. Phenotype of pituitary deficiency is highly variable ranging from panhypopituitarism to isolated GH deficiency. Eye anomalies such as anophthalmia and microphthalmia have been identified in patients with heterozygous OTX2 mutations since OTX2 plays a key role in retinal development (12). Brain MRI of patients



with this mutation is variable as well, showing normal or hypoplastic pituitary, inconstant ectopic posterior pituitary and Chiari malformation. Chiari malformations are complex structural malformations ranging from cerebellar tonsillar herniation through the foramen magnum to the complete absence of the cerebellum (9).

### **3.2.2. SOX2 and SOX3**

SOX2 is a member of the HMG transcription factors related to SRY (Sex determining region Y). It is expressed in Rathke's pouch and throughout the development of both anterior pituitary and diencephalon. It is necessary for normal brain, pituitary, eyes and inner ear development. Mutations in SOX2 have been associated with HH, bilateral microphthalmia, corpus callosum hypoplasia, SOD and inconstant mental retardation. Of the pituitary abnormalities, GH, TSH and ACTH deficiencies have been associated with this mutation and pituitary hypoplasia is present in 80% of the patients (12).

SOX3 dosage is as well critical for normal hypothalamic and pituitary development. Patients with duplication of SOX present with IGHD while patients with whole gene duplications/deletions present with anterior pituitary hypoplasia, absent pituitary stalk and ectopic neurohypophysis (12). In these patients, intellectual disability is frequently reported. Due to significant male predominance, X-linked transmission is suggested.

### **3.2.3. PITX2**

PITX2 is a member of homeobox genes. It is expressed in Rathke's pouch and anterior and intermediate pituitary lobes. It is preferentially expressed in gonadotropes and thyrotropes. Mutations in this gene have been associated with Axenfeld–Rieger syndrome characterized by anomalies in the eye (coloboma, increased risk of glaucoma), dental hypoplasia, protuberant umbilicus and brain abnormalities. Inconstant pituitary deficiencies have been reported, most commonly associated is GH deficiency (3, 9). In patients with this syndrome, at least six different mutations in PITX2 have been found.

### **3.2.4. ARNT2**

The role of Aryl hydrocarbon receptor nuclear translocator 2 (ARNT2) in pituitary development has not yet been precisely defined. According to (18), involvement of this gene in CPHD was identified through exome sequencing in a large consanguineous Saudi Arabian family in which

6 children presented with central diabetes insipidus and corticotroph deficiency shortly after birth. Four of them had associated TSH deficiency as well and 2 GH deficiency while 1 presented with gonadotroph deficiency and undescended testes. On brain MRI, hypoplastic anterior pituitary and pituitary stalk interruption, hypoplastic frontal and temporal lobes, thin corpus callosum were seen. All of the children were dysmorphic with prominent forehead, deep set eyes, deeply grooved philtrum, retrognathia and progressively appearing microcephaly. Hydronephrosis, vesico-ureteral reflux and neurogenic bladder were also present. It was determined that the parents were heterozygous for this mutation while children were homozygous.

### **3.3. Skeletal anomalies**

#### **3.3.1. LHX3**

LHX3 is a member of LIM class of homeodomain proteins and expression of this transcription factor persists in the mature pituitary gland and is essential for formation of gonadotrophs, thyrotrophs, somatotrophs and lactotrophs. Patients with mutation in LHX3 therefore present with GH, TSH and FSH/LH deficiency and ACTH deficiency is present in 58% of the mutations. Pituitary MRI is normal in 10% of patients while in others pituitary aplasia or hypoplasia can show (9). According to (12), mutations affecting entire gene or protein, LIM domains or the homeodomain present with syndromes involving the nervous and skeletal systems. More precisely, they can include the following: short neck with abnormal head and neck rotation (70% of cases), vertebral abnormalities (50% of cases) such as rigid cervical spine, flattened lumbar vertebrae, thoracic kyphosis, progressive scoliosis and hearing defects (50% of cases). Commonly, patients present with mental deficiencies. Expression of LHX3 in defined regions of the sensory epithelium of the developing ear and in developing motor neurons is the cause of above mentioned clinical manifestations (9).

### **3.4. Cerebellar anomalies**

#### **3.4.1. LHX4**

Both pituitary deficiencies and brain MRI of patients harbouring mutations in LHX4 present with wide phenotypic variability. Pituitary deficiencies can range from IGHD to complete panhypopituitarism while brain MRI can show pituitary hypoplasia, hypoplasia of corpus callosum or Chiari malformations (9,12). A mutation in this gene was described by (19) where

patients presented with GH, TSH and ACTH deficiencies associated with hypoplastic pituitary, stalk interruption syndrome and extrapituitary abnormalities: pointed cerebellar tonsils and poorly developed sella turcica. This phenotype was expressed in a fully penetrant manner over three generations.

### 3.5. Multisystemic syndromes in which hypopituitarism is a significant component

An association has been established between anterior pituitary hormone deficiency and common variable immune deficiency which is a heterogeneous disorder characterized by decreased concentration in all immunoglobulin types and a predominant T cell disorder making patient susceptible to bacterial infections. This association was named Deficient anterior pituitary with variable immune deficiency, DAVID syndrome. ACTH deficiency is most commonly associated with this disorder but partial GH and TSH deficiencies have been reported as well (12, 16). Mutations in NFKB2 gene (Nuclear Factor of Kappa Light Polypeptide Gene Enhancer in B-Cells) have been identified to cause this disorder. Precise mechanism how this factor leads to endocrine deficits remain unclear.

CHARGE syndrome is an autosomal dominant disorder. CHARGE is an abbreviation for clinical features of this disorder: coloboma, heart malformations, choanal atresia, retardation of growth and development, genital and ear abnormalities. Gregory et al. (20) describe two patients with CHARGE syndrome: in one patient associated endocrine abnormalities were GH deficiency and anterior pituitary hypoplasia and ectopic posterior pituitary and in other GH, TSH, ACTH, LH/FSH deficiencies with the same MRI abnormalities. Mutations in CHD7 occurring in 65% of patients with CHARGE syndrome are reported in septo-optic dysplasia as well. CHD7 mutations are not common in pituitary insufficiency or septo-optic dysplasia without features of CHARGE.

Table 2. Gene mutations leading to syndromic CPHD and associated phenotypes.

Table 2:

<b>Transcription factor</b>	<b>Pituitary hormone deficiencies</b>	<b>Phenotype</b>
<b>SHH</b>	CPHD	HPE, eye, dental anomalies
<b>GLI2</b>	CPHD	HPE, polydactyly, ectopic posterior pituitary
<b>HESX1</b>	IGHD or CPHD (in 50% of patients)	SOD, hypoplastic anterior pituitary

<b>FGF8</b>	FSH, LH GH, TSH, LH deficiency	Ear hypoplasia, dental agenesis, cleft palate, distal limb malformations, SOD, HH, Kallmann syndrome, absent corpus callosum
<b>FGFR1</b>	CPHD	Absent corpus callosum, SOD, HH
<b>PROK2 and PROKR2</b>	CPHD	PSIS, HH, Kallmann syndrome, SOD
<b>OTX2</b>	IGHD-panhypopituitarism	Chiari malformations, ectopic posterior pituitary, hypoplastic pituitary, eye malformations – anophthalmia, microphthalmia
<b>SOX2</b>	GH, TSH, ACTH deficiencies	HH, bilateral microphthalmia, corpus callosum hypoplasia, SOD, pituitary hypoplasia, mental retardation
<b>SOX3</b>	CPHD	anterior pituitary hypoplasia, absent pituitary stalk and ectopic neurohypophysis
<b>PITX2</b>	Inconstant pituitary deficiencies	Axenfeld–Rieger syndrome
<b>ARNT2</b>	CPHD	Eye anomalies, hypoplastic anterior pituitary, thin pituitary stalk, microcephaly, renal anomalies, dysmorphic facial features
<b>LHX3</b>	GH, TSH, FSH/LH, ACTH deficiencies	pituitary aplasia or hypoplasia, : short neck with abnormal head and neck rotation, vertebral abnormalities (rigid cervical spine, flattened lumbar vertebrae, thoracic kyphosis, progressive scoliosis), hearing defects
<b>LHX4</b>	IGHD - panhypopituitarism	hypoplastic pituitary, stalk interruption syndrome, pointed cerebellar tonsils, poorly developed sella turcica

## 4. PURELY ENDOCRINE PHENOTYPE OF CPHD

Mutations in late acting transcription factors produce “pure” endocrine phenotype, meaning there are no manifestations besides pituitary hormone deficiencies. The transcription factors that influence only the development of pituitary cell lineages are PROP1 and POU1F1.

### 4.1. PROP1

Mutations in the PROP1 gene are responsible for a high proportion of multiple or combined pituitary hormone deficiencies. PROP1, also known by the name of Prophet of Pit, is a transcription factor which induces the expression of POU1F1 (another early-acting transcription factor, discussed later), meaning that expression of PROP1 is necessary for the later expression of POU1F1. Patients harbouring PROP1 mutations present with CPHD including GH, TSH, PRL, ACTH, LH and FSH deficiencies (21), although there is significant variability of the hormonal pattern. Considerable variations in timing and severity of hormone deficiencies are seen even among siblings which have the same homozygous mutation (21). In most cases, GH and TSH deficiencies are present at diagnosis. Short stature is generally the first reported symptom, probably due to combined GH and TSH deficiencies. Growth failure usually develops within the first year of life and becomes prominent in early childhood, mainly between 1.5 and 3 years. LH and FSH deficiencies are noted at the onset of puberty due to gonadotroph function progressively declining and children presenting with lack of pubertal development or failure to enter complete puberty (21, 22).

Decrease in ACTH, and consequently cortisol, arises in many patients later in life (mean age at diagnosis 25 years) (21) and it is suggested to be caused by a progressive lack of paracrine signals from dysfunctional cell lineages surrounding corticotroph cells and due to the dysfunctional PROP1 role in cell lineage maintenance and hormone expression (2).

There is even a subset of patients with PROP1 mutations, although rarely reported, presenting with IGHD and patients with retained somatotrope function able to attain normal final height without GH replacement therapy (23).

Homozygous carriers of PROP1 mutations frequently present with early hypogonadism with micropenis and cryptorchidism or complete lack or delayed puberty in later adolescence due to gonadotrope dysfunction. Although recent investigations in rodent models have demonstrated active role of PROP1 in gonadotrope specification, differentiation and maintenance, it is challenging to prove how big of a role to this phenotype play in the LH/FSH independent mechanisms due to the fact that signs of hypogonadism in neonates have been observed in conditions like IGHD and GH insensitivity (2, 22).

Dysfunction of thyrotropes, somatotropes, lactotropes in patients with homozygous PROP1 mutation reflects the lineage specifying actions of PROP1 established during pituitary development. Unlike these, mechanisms that lead to FSH/LH and ACTH deficiency are still speculative and variability of the hormonal pattern is particularly evident for these hormones (2).

Intrapituitary masses are commonly found in patients with mutations in PROP1. These masses are initially solid and progress to cystic. They warrant no surgical interventions because they eventually regress over time (24). These pituitary enlargements are suggested to originate from the intermediate lobe and are described as nonenhancing mass lesions situated between normal enhancing anterior lobe and the neurohypophysis (25).

Crorrea et al. (21) described 14 patients, out of which 11 showed hypoplastic anterior pituitary. The pituitary gland size varied over time from hyperplastic to normal in only one patient, while two had normal-sized pituitary gland. Furthermore, unlike in patients with CPHD with associated extrapituitary manifestations, pituitary stalk is intact and posterior pituitary lobe appears in normal position.

Due to possible development of ACTH deficiency which is potentially life threatening, permanent surveillance is required.

#### **4.2. POU1F1**

POU1F1 (previously known as Pit-1 or GHF1) gene mutations lead to deficiency of GH, TSH, PRL (26). When compared with PROP-1 mutation phenotype, it can be seen that ACTH and gonadotropins are not affected by mutations of this transcription factor.

GHD is typically severe and if left untreated leads to severe short stature within the first year of life. TSH deficiency is common to most, but not all patients and it varies in severity and ranges from mild central hypothyroidism to severe congenital hypothyroidism (26, 11)

Most of the POU1F1 mutations are recessive but one dominant mutation is proven to be very common. This dominant mutation might result in severe intrauterine hypothyroidism in case affected mother does not receive appropriate thyroid hormone replacement during pregnancy. According to two cases reported on this topic where adequate supplementation is not given, infants experienced severe respiratory distress and were developmentally delayed (11).

Size of anterior pituitary is normal or small. Variability in the morphology of the anterior pituitary and variability in endocrine presentation does not correlate with the mutation site, meaning that even familial cases having the same mutation demonstrate differently sized anterior lobes (2).

## **5. DIAGNOSIS AND WORKUP**

As previously noted, congenital hypopituitarism presents with various non-specific features but a combination of neonatal hypoglycemia, micropenis, cholestasis or growth failure help guide the differential diagnosis toward hypopituitarism. Moreover, family history of hypopituitarism suggests that a fetus is at an increased risk. In case of persisting hypoglycemia with early onset, requirement for high glucose infusion rates to maintain normoglycemia and inability to tolerate normal interval between feedings, measuring insulin in a child is useful. This can help to exclude hyperinsulinism and to focus on hypopituitarism (11).

Diagnosis of hypopituitarism CPHD should be suspected in children with extrapituitary midline defects such as a single central incisor, cleft lip, and/or palate or agenesis of the corpus callosum. Cleft palate or a single central incisor may be identified prenatally, raising consideration of hypopituitarism associated with holoprosencephally (10).

Diagnosis of CPHD is a dynamic process and physicians need to keep an open mind. According to (27), out of 716 GH-treated patients with what was initially thought as isolated GH deficiency, development of CPHD was found during follow-up in about 10% of cases. The most frequent additional hormone deficiencies were those of TSH and gonadotropins.

### **5.1. Diagnosing hormone deficiencies**

The diagnosis of combined pituitary hormone deficiency requires presence of GH deficiency and at least one other pituitary hormone.

Diagnosis of GH deficiency remains problematic because of the difficulty in measuring physiologic GH secretion since concentrations of GH are low throughout the day except for few secretory peaks. Therefore, single measurement of random GH concentration is not of significant diagnostic value except in infants. In older children, provocative tests can be done to stimulate the secretion of GH. GH secretion is stimulated using insulin, glucagon, levodopa or clonidine (11). Serum concentration of GH less than 7-10 ng/dL on two provocative tests suggests a diagnosis of GH deficiency. These tests are associated with a high false positive rate (28). Furthermore, stimulation tests are contraindicated in newborns and young infants. Indirect measurements of GH secretion such as insulin-like growth factor-1 (IGF-1) and insulin-like growth factor binding protein-3 (IGF-BP3) can be used as well. These are key surrogate markers of growth hormone and along with delayed skeletal maturation assessed

by bone age X-ray imaging, they can help in diagnosing GH deficiency (1). An alternative to stimulation test to diagnose GH deficiency in infancy is assay of random specimen obtained during the first week and a specimen obtained at the time of hypoglycemia (11). According to (29), in the presence of clinical evidence, the diagnosis of neonatal GHD can be confirmed during the first week of life by a single randomly taken GH level less than 7 ug/L with 100% sensitivity and 98% specificity. Samples of dried blood spots on filter paper cards used for newborn metabolic screening were used.

Diagnosis of central hypothyroidism is supported by findings of low fT4 levels with an inappropriately low TSH level. It is important to note that newborn screening for congenital hypothyroidism includes screening for elevated TSH, therefore individuals with central hypothyroidism who have low/normal TSH are not detected by these screens (28).

Central adrenal insufficiency (CAI) is characterized by inappropriate ACTH secretion resulting in abnormal adrenal cortisol production. Diagnosis is supported by low cortisol levels along with low or inappropriately normal ACTH levels (1). Early morning cortisol sampling is indicated after a diurnal pattern of cortisol levels is established around 2 months of age (11). Cortisol level below 3mg/dl is indicative of adrenal insufficiency while values greater than 13mg/dl make the diagnosis unlikely (30). Often, early morning cortisol level falls in an intermediate range, requiring dynamic testing. Dynamic testing includes administration of cosyntropin (synthetic ACTH) to directly stimulate adrenal cortisol release. Baseline ACTH and cortisol samples are obtained and then cosyntropin is administered intravenously, followed by cortisol samples drawn at 30 and 60 minutes later (8). If the ACTH deficiency is severe and lasting for a long period of time, it will have induced secondary adrenal atrophy and stimulation with corticotrophin will not induce a normal response. However, in patients with moderate or recent ACTH deficiency where adrenocortical atrophy is incomplete or absent, this test may not show values indicative of adrenal insufficiency (30). It is also important to note that newborns have adequate adrenal reserve that allows temporary normal cortisol response to synthetic ACTH injection after birth. According to Mehta et al (31), a combination of early morning serum cortisol level greater than 6.3 mg/dL and a 30-minute serum cortisol level greater than 20 mg/dL would ensure that no child with ACTH deficiency would be missed and experience serious consequences. These results could however lead to over diagnosis. When the diagnosis of ACTH deficiency is made, it is important to rule out other pituitary hormone deficiencies because isolated ACTH deficiency is rare (8).



The diagnosis of LH and FSH deficiencies in childhood can be difficult as throughout most of the first 10 years of life (with exception of 'mini puberty') the serum concentrations of LH and FSH in children are naturally low (4). Mini puberty is a surge in gonadotrophins and sex steroids which lasts up to 6 months of life and it provides a window of opportunity for testing. In male infants, a combination of detailed evaluation of the external genital phenotype together with assessment of LH, FSH and sex steroid levels during the postnatal surge of gonadotropins facilitates the diagnosis of hypogonadotropic hypogonadism at an early age (1, 32).

Testing can be done during the normal age of puberty as well when it should be performed early mornings using highly sensitive assays. Low sex steroid levels with low or inappropriately normal gonadotropin values is suggestive of diagnosis (1).

## **5.2. Role of MRI**

MRI enables detailed visualization of the pituitary gland, providing high resolution multi planar and spatial images allowing detailed and precise anatomical study with ability to differentiate between anterior and posterior lobe. Neurohypophysis or posterior pituitary is normally seen as a bright spot caused by storage of vasopressin-neurophysin II copeptin complexes. This bright spot or hyperintensity is a sign of neurohypophysial functional integrity. This should be seen in the posterior part of the sella turcica and if present somewhere else, it is a sign of ectopic posterior pituitary (4).

Anterior pituitary size and contour and posterior pituitary bright spot can be well visualized in sagittal T1 images. Further information can be acquired through dynamic imaging with contrast which provides information about the vascular component of the pituitary stalk. This is important due to the fact that patients with agenesis of the pituitary stalk run a greater risk of developing multiple hormone deficits and it is important to follow-up these patients.

When assessing CPHD it is important to determine whether any of the following is seen on MRI: ectopic posterior pituitary (EPP), which can reside in the hypothalamus or at any point along the pituitary stalk, anterior pituitary hypoplasia, absence, or attenuation of the stalk connecting hypothalamus and the pituitary. Previously mentioned occurrences are known as pituitary stalk interruption syndrome (PSIS), which is a feature of CPHD. It can be seen as well in patients suffering from IGHD, and in that case, these patients are at an increased risk for progression to CPHD (11). Out of examined 101 pediatric patients with hypopituitarism, 59% had EPP. Out of those with EPP, 49% had CPHD (33).

MRI can be useful, together with clinical features in guiding the genetic testing. In cases where small pituitary gland, enlarged empty sella, pituitary hyperplasia or intrasellar or suprasellar mass are found in the context of CPHD, molecular analysis of Pit-1, Prop-1, Hesx-1 or Lhx-3 should be performed.

### **5.3. Genetic testing**

The recognition of the underlying molecular defect is important not only for satisfying scientific interest but also for genetic counselling for which the localization of the underlying molecular defect is a prerequisite (10). The great majority of CPHD cases are sporadic although there are forms of CPHD that have autosomal recessive, autosomal dominant, or X-linked modes of inheritance. Unfortunately, there are no clinical or endocrinologic differences that consistently differentiate genetic forms of CPHD and the more common acquired form of CPHD (34).

A definitive hint toward genetic cause of hormone deficiency would be familial cases involving multiple affected individuals. Genetic cause of CPHD is usually suspected in cases where the phenotypic appearance is compatible with congenital defect, in cases where there are associated central nervous system anomalies and findings of ectopic posterior pituitary (34). In case of normal parents and an affected sibling, possibility of a recessive or polygenic disorder should be aroused. Also, an affected parent may have passed on a dominant mutation in the POU1F1 gene. X-linked inheritance should be considered in cases with affected maternal uncle (11).

It is very important to consider whether the cause is sporadic or familial since probability of finding a causative gene mutation is much higher in familial cases.

Pituitary imaging represents a useful element to guide genetic screening of CPHD together with hormonal pattern and extrapituitary phenotype, therefore, performing a pituitary MRI is suggested when considering genetic analyses.

PROP1 mutation has to be carefully considered in a patient with GH, TSH, prolactin and gonadotropin deficiency, especially when no alterations in the pituitary stalk or posterior hypophysis are detected at MRI. A POU1F1 mutation is suggested by the finding of GH and prolactin deficiency, with severe growth retardation and variable degrees of TSH deficit. A HESX1 mutation is suspected in a patient with septo-optic dysplasia and variable degrees of pituitary hormone deficiency, ranging from isolated GHD to panhypopituitarism. Mutations of

LHX3 gene have to be suspected in individuals with variable degrees of anterior pituitary hormone deficiencies and extra-pituitary clinical manifestations, such as limited neck rotation and perceptive deafness. The neuroradiological finding of a poorly developed sella turcica, in a child with congenital CPHD, should arouse the suspicion of a LHX4 mutation (35).

Although hormonal patterns can help guide genetic testing, these mutations are characterized by variable degrees of hormone deficits, ranging from IGHD to panhypopituitarism and this complex hormonal picture may be complicated further by development of additional hormonal deficiencies later in life. Furthermore, penetrance and expressivity can be variable and an affected child may have inherited a variant from an apparently unaffected parent (36).

In case where mutation of a single gene is the most likely etiology, traditional or Sanger sequencing of the gene should be performed (36). However, clinical evaluation of the patient with CPHD will most likely result in many potential genetic etiologies so a multi-gene panel using Next generation sequencing can be very useful. Gene by gene screening is unlikely to identify digenic or multigenic disease unless all known genes are investigated in each patient. Next generation sequencing may cover only few genes or it may include coding regions of all genes, known as whole exome sequencing (WES). WES is currently the most commonly used massively parallel sequencing technique. It examines the exons of all known protein-coding genes simultaneously and offers a powerful approach to rapidly screen for candidate disease-causing mutations. With reduced costs and increased application of next generation sequencing techniques novel genes and variants are expected to be discovered. Widespread application of these methods will result in better molecular diagnosis of CPHD and provide new insight into pituitary organogenesis (5, 36).

## **6. MANAGEMENT AND FOLLOW UP**

Appropriate hormone replacement therapy is the main goal in patients with CPHD and therefore precise recognition of deficient hormones is important.

Growth hormone deficiency is treated with daily subcutaneous injection of recombinant GH. In order to achieve the best growth response, therapy should be started as soon as the diagnosis of GH is established. Dose of recombinant GH is calculated based on body weight and after initiating treatment, growth velocity and IGF-1 levels should be monitored. Some adverse reactions can develop but usually this treatment is well tolerated (1). Adverse reactions include idiopathic intracranial hypertension, slipped capital femoral epiphysis and insulin resistance due to growth hormone antagonizing insulin effects in glucose and lipid metabolism through stimulation of glycogenolysis and lipolysis (37).

Adequate and timely levothyroxine (LT4) treatment is crucial for normal neurodevelopment in the first 3 years of life. It is important to first exclude adrenal insufficiency since LT4 treatment increases basal metabolic rate and enhances cortisol clearance, and therefore, may precipitate an adrenal crisis. Free T4 levels are used for monitoring and the aim is to maintain value in the upper half of the normal range (1).

Cortisol replacement is initiated using hydrocortisone since it is easy to titrate and has less suppressive effects on growth compared with more potent longer acting glucocorticoids such as dexamethasone or prednisone. Recommended physiologic replacement dose of hydrocortisone in pediatric patients is approximately 10-12.5 mg/m<sup>2</sup>/day divided into two or three doses. When treating CPHD, it is important to have in mind that these patients are more prone to hypoglycemia so dosing 3 times a day is recommended (8). Patients must be educated on 'stress dosing' ranging from 2 to 10 times the maintenance dose based on severity, and a medic alert identifier should be worn (1).

In newborn male infants with congenital gonadotropin deficiency, treatment is focused on appropriate testicular descent and penile growth. Surgical correction is indicated to correct cryptorchidism. Three intramuscular injections of a long-acting testosterone ester at a dose of 25mg should be given monthly, followed by another three doses if a satisfactory increase in penile length (>0.9 cm) has not occurred (32).

In adolescence, replacement is started around the time of mean entrance into puberty for the patient's sex. Estrogen is available as either a transcutaneous patch or pill. Transcutaneous method bypasses first-pass hepatic metabolism seen with oral medication and therefore it may result in better replacement with lower risk. Doses start small and are increased periodically to mimic the natural progression of secondary sex characteristics. Breakthrough vaginal bleeding may be present once the uterine lining has received sufficient estrogen stimulation and at this time progesterone is typically added to stabilize the lining and is periodically stopped to allow regular menses. Testosterone replacement is commonly initiated with a long-acting ester at a starting dose of 50 mg every 4 weeks with gradual dose increases until adult dosing is achieved (1).

## **7. CONCLUSION**

Over the past 30 years, around 30 genes causing CPHD have been identified. Discovery of new genes helps in understanding of the development of hypothalamic-pituitary axis, cellular

and molecular regulation of hormone production and secretion and genetic basis for endocrine disorders (5). Clinical picture of CPHD may present at birth or shortly afterwards, with varying combinations of hypoglycemia and prolonged cholestatic neonatal jaundice in both sexes and microphallus and/or bilateral cryptorchidism in boys. In most cases, however, diagnosis is suspected during the first years of life, owing to the finding of a severe and progressive growth and bone age retardation. Extra-endocrine clinical manifestations include craniofacial defects, such as septo-optic dysplasia, holoprosencephaly, corpus callosum aplasia, ocular abnormalities, limited neck rotation and short cervical spine. The decision on which genes should be tested and in which order should be guided by hormonal and imaging phenotype, the presence of extrapituitary abnormalities and the frequency of mutation for each gene in the patient-referring population (38).

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