Chapter 12
Combined Pituitary Hormone Deficiency

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The Murine Pituitary Development: A Useful Tool to Decode Human Pituitary Development

Human pituitary development is assumed to follow more or less closely the murine pituitary development, and this is why the murine model currently represents the most appropriate model to determine the major temporospatial interactions between signaling pathways and transcription factors leading to a mature endocrine organ [1, 2]. Pituitary development in humans is imperfectly known, and all the steps described in the following lines are based on our knowledge of murine pituitary development.

Anterior and posterior pituitary lobes have two different embryonic origins: the anterior lobe is derived from oral ectoderm, whereas the posterior lobe is derived from neurectoderm. Even if close connections exist between both structures, we will only focus on the development of the anterior lobe and the mature pituitary. No study to date on human pituitary deficiency has identified strong connections and phenotypic associations that include anterior pituitary deficiencies and congenital diabetes insipidus (except for the only reported aryl hydrocarbon receptor nuclear translocator (*ARNT2*) mutation, as described later).

Briefly, anterior pituitary ontogenesis begins early during brain neurogenesis, around embryonic day (e) 7.5 in the mouse, corresponding to the first visualization

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of the pituitary placode [3]. At e9, the placode forms the rudimentary Rathke's pouch, under the control of signaling molecules issued from the infundibulum (bone morphogenetic protein 4 (Bmp4) and fibroblast growth factor 8 (Fgf8)). Definitive Rathke's pouch is observed at e11.5 [4]. Progenitors around the lumen move progressively to the developing pituitary and differentiate under the control of several factors including SRY-box (Sox)2, Sox9, and Isl Lim homeobox (Isl)-1, among others; the majority of these have not been identified as causative factors for pituitary deficiencies, suggesting that they are either crucial (and would lead to early death if abnormal) or that other pathways can be used if they are abnormal [5–7]. This first step leading to terminal differentiation of the pituitary is possible due to a tightly controlled temporospatial gradient of morphogenic factors from different origins, the diencephalon (Bmp4, Fgf8, 10 and 18, Wnt5a), the ectoderm (Isl1, Bmp2, sonic hedgehog (Shh), Wnt 4), the ventral mesoderm (chordin, Bmp2) [8], or the pituitary cells (Table 12.1).

At e11.5, α-subunit is expressed in the rostral tip [9], followed by adrenocorticotropin (ACTH) (e12.5), thyrotropin (TSH)β (e14.5), proopiomelanocortin (Pomc)

Table 12.1 Main differences between human and murine phenotypes and partial/complete loss of function of the major proteins encoded by genes involved in combined pituitary hormone deficiencies

	Murine phenotype	Human phenotype	Transmission
POU1F1	GH, TSH, Prl deficiency Pituitary hypoplasia	GH, TSH, Prl deficiency. Pituitary hypoplasia	Recessive (murine): recessive or dominant (human)
PROP1	GH, TSH, Prl deficiency	GH, TSH, Prl, LH/FSH deficiencies; inconstant ACTH deficiency. Inconstant transient pituitary hyperplasia and then hypoplasia	Recessive (murine and human)
HESX1	Variable phenotype, midline anomalies. Eye anomalies. Pituitary hypoplasia or hyperplasia	Variable pituitary deficiencies (from isolated GH deficiency to panhypopituitarism); normal or hypoplasic pituitary. Septo-optic dysplasia	Recessive (murine): recessive or dominant (human)
OTX2	Severe anomalies of anterior brain structures, pituitary dysmorphology	Variable pituitary deficiencies (from isolated GH deficiency to panhypopituitarism). Normal or hypoplasic pituitary, normal or ectopic posterior pituitary. Inconstant brain anomalies	Recessive (murine and human)
LHX3	Pituitary aplasia	GH, TSH, LH/FSH deficiencies; inconstant ACTH deficiency. Hypoplasic or hyperplasic pituitary. Neck rotation anomalies; deafness	Recessive (murine and human)
LHX4	Hypoplasic pituitary	Pituitary deficiencies, extrapituitary anomalies	Recessive (murine), dominant (human)

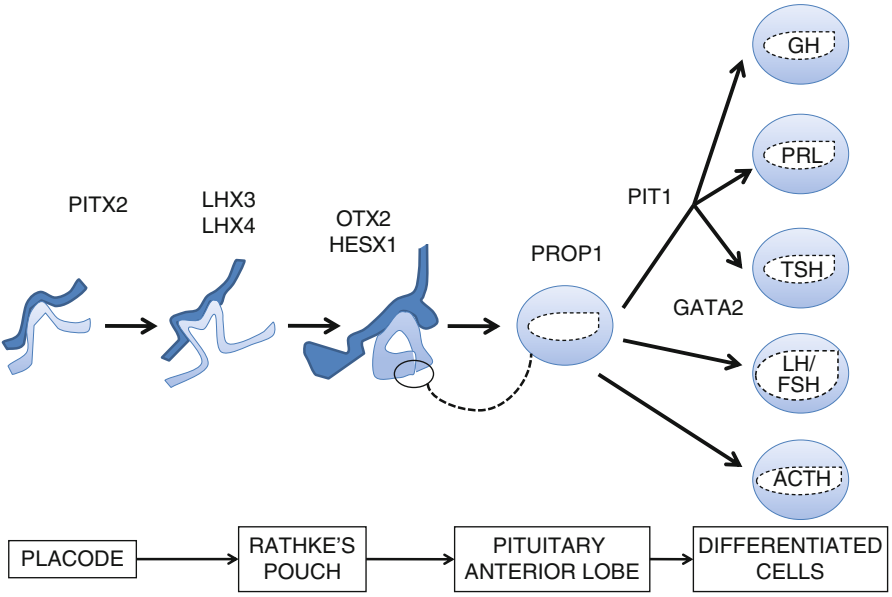

Fig. 12.1 Simplified scheme representing the main transcription factor expression during pituitary development. Note that early transcription factor dysfunction is associated with pituitary and extrapituitary anomalies, whereas late transcription factor (PIT-1, PROP1) dysfunction is associated with pure pituitary phenotype

(e14.5, intermediate lobe), growth hormone (GH) and prolactin (Prl) (e15.5) [10], luteinizing hormone (Lh)β (e16.5), and finally follicle-stimulating hormone (Fsh)β (e17.5). Precise mechanisms leading to this differentiation and the formation of pituitary cell networks remain incompletely understood. Pituitary specific or nonspecific transcription factors are involved in a timely manner during these steps of differentiation, early acting such as LIM homeobox (Lhx)3, Lhx4, paired-like homeodomain transcription factor (Pitx)2, Hesx1 (also known as Rpx), or ARNT2 [11] or late-acting such as prophet of Pit-1 (Prop1) and Pou1f1 (Pit-1). Early acting transcription factors are also involved in the development of other organs (e.g., the eye, inner ear), and their defects lead to extrapituitary anomalies, whereas alterations of late-acting transcription factors usually lead to a pure pituitary phenotype. A summarized scheme of the timing of expression of the transcription factors known to be involved in CPHD is given in Fig. 12.1.

Early Acting Transcription Factors: The Pituitary Phenotype Is Usually Not Alone

Anomalies of these transcription factors are characterized by a wide range of phenotypes, usually including anterior pituitary hormone deficiencies, extrapituitary abnormalities, and malformations such as pituitary stalk interruption syndrome

(PSIS) or midline defects. These complex phenotypes are due to the non-pituitary-specific expression of these transcription factors, which are also involved in the development of the forebrain and related midline structures such as the hypothalamus. To make the description easier, we focused on the phenotypic traits that should guide the clinician to certain transcription factors.

Etiological Possibilities in Patients Carrying Pituitary Deficiency and Midline Anomalies: HESX1, GLI2, FGF8 and FGFR1, PROK2, and PROKR2

What do we call midline anomalies? It is a large group of diseases from pituitary stalk interruption syndrome to septo-optic dysplasia (SOD) and holoprosencephaly. Pituitary stalk interruption syndrome is defined on brain MRI by the association of an absent or thin pituitary stalk, pituitary hypoplasia, and/or ectopic posterior pituitary [12]. As only 30 % of patients with PSIS have a history of traumatic event, it is likely that a high number of cases are actually due to genetic anomalies. Septo-optic dysplasia is defined by at least two of the following criteria: septum or corpus callosum agenesis, optic nerve hypoplasia, and pituitary deficiencies [13]. Holoprosencephaly is a complex brain malformation, affecting both the brain and face (cyclopia, median or bilateral labial and/or palatal cleft, hypotelorism or a single median incisor in milder cases) due to an abnormal division of the prosencephalon between days 18 and 28. Intellectual disability is frequently associated. Recent studies emphasize the continuum between these different genetic causes leading to phenotypes of variable severity depending on the degree of abnormal development of the anterior brain [14–16]. This likely explains why, for any given pathway or transcription factor, the phenotype can be highly variable from mild to extremely severe. This group mainly includes anomalies of the paired transcription factor HESX1, and few novelties less well known such as GLI2, or pathways previously thought to be only involved in isolated hypogonadotropic hypogonadism. We will see, however, in the next paragraph that other transcription factors, more likely involved in eye development, can also lead to midline anomalies, which makes this classification difficult to perform.

HESX1

Hesx1 is a paired homeodomain transcription factor that has been well characterized over the last 15 years. It is a major actor in pituitary development as its expression and then inhibition are crucial at given time points to allow the formation of a mature Rathke's pouch. The expression profile of Hesx1 perfectly illustrates the complexity of pituitary development. For instance, decreased expression of Hesx1

at e13 in mice is necessary for Prop1 and secondarily Pou1f1 expression, two late transcription factors necessary for proper differentiation of GH-, TSH-, and Prl-secreting cells [17–20]. Appropriate expression of other early acting transcription factors such as Lhx1, Lhx3, or Six3 (some being involved in human disease) is also necessary for early proper Hesx1 expression [21]: the lack of Hesx1 in mice (homozygous inactivation *Hesx1*$^{-/-}$) indeed leads to a very severe phenotype with corpus callosum aplasia and ectopic posterior pituitary. In humans, HESX1 mutations can lead to a wide range of phenotypes: 16 *HESX1* mutations have been reported [17, 22–30], the homozygous anomalies (40 % cases) usually leading to a more severe phenotype [31]. GH deficiency is constant; other pituitary deficiencies are reported in 50 % cases. Optic nerve anomalies are the other major phenotypic sign, observed in 30 % cases. One should not consider, however, that SOD is always due to *HESX1* mutations, as only 1 % cases have actually been linked to this genotype [31–34]. Brain MRI usually reveals pituitary hypoplasia (80 % cases) and midline anomalies such as ectopic or non-visible posterior pituitary in 50–60 % cases and corpus callosum agenesis or hypoplasia in 25 % cases.

Sonic Hedgehog and GLI2

Sonic hedgehog (SHH) signaling pathway is involved in the early steps of pituitary development: *SHH* mutations have been reported in patients with severe forms of isolated holoprosencephaly [35]. SHH targets, GLI transcription factors, have also been involved in CPHD: *GLI2* heterozygous mutations have been reported in patients with holoprosencephaly or with pituitary hormone deficits and less severe midline craniofacial anomalies and pituitary hypoplasia, corpus callosum agenesis, or ectopic posterior pituitary on brain MRI; some individuals also have polydactyly.

Pathways Known to Be Involved in Hypogonadotropic Hypogonadism

FGF8 and FGFR1

FGFR1 and *FGF8* heterozygous mutations were first reported in 10 % of Kallmann syndrome and 7 % of normosmic hypogonadism [36]. Pituitary MRI showed normal or hypoplastic anterior pituitary and inconstant ectopic posterior pituitary. Penetrance was incomplete [37, 38]. However, the expression of Fgf8 and Fgfr1 in the ventral diencephalon is necessary for proper Rathke's pouch formation, temporospatial pattern of pituitary cell lineages, and the development of extrapituitary structures [39]. This explains why other anomalies were then reported such as ear hypoplasia, dental agenesis, cleft palate, and distal limb malformations. Finally, *FGFR1* and *FGF8* mutations have also been reported in patients with SOD, with about 4 % prevalence [14].

PROK2 and PROKR2

Prokineticin pathway is known to be involved in portal angiogenesis and neuronal development and migration [40]: this suggested its potential involvement in pituitary stalk development. *PROK2* and *PROKR2* mutations have recently been reported in a cohort of patients with pituitary deficiencies, anterior pituitary hypoplasia or aplasia, and PSIS [15]. Mutations in these genes were also reported thereafter in patients with SOD, and inconstant additional brain abnormalities, such as cerebellar hypoplasia, Dandy-Walker cyst, or focal abnormality of mesial frontal cortex [16].

Etiological Possibilities in Patients Carrying Pituitary Deficiency and Eye Anomalies: OTX2, SOX2, PITX2, ARNT2

Whereas *OTX2* mutations seem to play an important role in CPHD, the other factors reported here have been recently described or do not seem to be involved in a large number of patients. This explains why they are usually not screened in patients, except in case of a specific phenotypic sign associated to CPHD.

OTX2

Otx2 is a paired homeodomain transcription factor involved in the early steps of brain development. In mice, Otx2 is expressed from e10.5 to e14.5 in the ventral diencephalon, where it likely interacts with Hesx1, and from e10.5 to e12.5 in Rathke's pouch. Otx2 is also involved in gonadotropin-releasing hormone (GnRH) neuronal development [41]. In mice, homozygous inactivation of *Otx2* (*Otx2*$^{-/-}$) leads to a severe brain phenotype; heterozygous inactivation leads to a wide range of phenotype, with eye anomalies, inconstant holoprosencephaly, and usually pituitary hypoplasia. This phenotype is close to the one observed in humans: 25 heterozygous de novo *OTX2* mutations have been reported, including nine in patients with congenital hypopituitarism; the remaining 16 mutations were reported in patients with ophthalmic diseases and no mention of pituitary deficiency. Individuals can either present with isolated GH deficiency or panhypopituitarism and inconstant hypoplastic pituitary, ectopic posterior pituitary, and Chiari syndrome. There is no genotype/phenotype correlation [42–46].

SOX2

Sox2 is an "HMG DNA-binding domain" (similar to SRY gene) transcription factor. At e9.5, Sox2 expression is observed in the brain, the neural tube, the oral endoderm, the sensorial placodes, and the branchial arcs. At e11.5, Sox2 is expressed in Rathke's pouch and the future hypothalamus. Sox2 is then expressed in the periluminal

proliferative zone where it could be involved in the maintenance and function of pituitary progenitors [47]. At adult age, Sox2 is expressed in the periventricular zone of the lateral ventricles and in the dentate gyrus, but its precise role (promoting the differentiation of stem cells in injured pituitary?) is unknown. Homozygous inactivation is lethal in mice; heterozygous inactivation leads to increased perinatal death, epilepsy, and almost complete panhypopituitarism (corticotroph axis is usually functional); in contrast, eye anomalies are inconstant. The phenotype is different in humans: heterozygous de novo *SOX2* mutations have been observed in six patients with hypogonadotropic hypogonadism, bilateral microphthalmia, corpus callosum hypoplasia, and inconstant intellectual disability. Pituitary phenotypes included inconstant GH, TSH, or ACTH deficiencies, and pituitary hypoplasia in 80 % cases. Surprisingly, corpus callosum anomaly has been reported in one case [47].

PITX2

PITX2 is not the perfect example of a transcription factor to think about in patients with CPHD. Despite its obvious roles in pituitary development, only three patients have been reported as having GH deficiency and pituitary hypoplasia [48–50]. As shown in mice, it is probably because of compensatory mechanisms, at least in the pituitary, likely due to a close transcription factor, Pitx1. Pitx2 is a paired homeodomain transcription factor expressed in Rathke's pouch at e10.5 [51, 52] and pituitary anterior and intermediate lobes at e12.5. At adult age, Pitx2 is expressed in thyrotrophs and gonadotrophs [53]. Pitx2 expression is ubiquitous, as it has also been observed in the adult brain, eye, kidney, lungs, testis, and tongue [51, 54]. In humans, *PITX2* mutations have been reported in patients with Axenfeld-Rieger syndrome, which is characterized by anomalies in the ocular anterior compartment and systemic malformations (craniofacial dysmorphy, dental, and umbilical anomalies) [55, 56]. *PITX2* mutations should thus be screened in patients with this phenotype, keeping in mind that some pituitary deficiencies might be associated. It does not make sense to routinely screen for *PITX2* mutations in patients with CPHD.

ARNT2

A recent report described a large consanguineous family with eye abnormalities, congenital hypopituitarism, diabetes insipidus, and renal and central nervous system (CNS) anomalies, related to a defect in the helix-loop-helix transcription factor ARNT2. ARNT2 is known to be involved in the development of the hypothalamus, other CNS structures, the kidneys, and the eyes. All patients presented with a thin pituitary stalk, hypoplastic anterior pituitary, ectopic or nonvisualized posterior pituitary, hypoplastic frontal and temporal lobes, thin corpus callosum, and delay in brain myelination [11]. Precise roles of ARNT2 during pituitary and extrapituitary structure development are, however, imperfectly determined, and the search for other mutations in patients with CPHD has been negative to date.

Etiological Possibilities in Patients Carrying Pituitary Deficiency and Neurogenesis Anomalies: The LIM Domain Transcription Factors

LHX4 and LHX3 are two close transcription factors belonging to a large family of transcription factors known to be involved in the development of several structures. Several mutations of LHX4 and LHX3 have been reported for the last 10 years in patients with CPHD. In contrast, up to now, no mutation has been identified in patients with a pituitary phenotype in the other LIM domain transcription factors.

LHX4

Lhx4 is involved in the early steps of pituitary ontogenesis. In mice, Lhx4 expression has been reported in Rathke's pouch at e9.5 and in the anterior part of the pituitary at e12.5. A low expression is still observed at adult age [57, 58]. The phenotype of homozygous inactivation of Lhx4 in mice is lethal due to respiratory distress, whereas heterozygous inactivation is not symptomatic. The main difference with humans is actually the transmission mode of inheritance, as all human *LHX4* mutations are in a heterozygous state: 11 sporadic or familial *LHX4* mutations have been reported in 17 patients [59], with a wide intra- and interfamilial phenotypic variability in terms of pituitary phenotype (ranging from isolated GH deficiency to complete panhypopituitarism) [60, 61] and brain MRI (pituitary hypoplasia, inconstant ectopic posterior pituitary and sellar hypoplasia, corpus callosum hypoplasia, or Chiari syndrome). Of note, one patient carrying a 1q25 microdeletion (including *LHX4* deletion) also presented with a cardiac defect (but it was likely multifactorial).

LHX3

Lhx3 is the perfect example of how extrapolating a human phenotype from a mouse phenotype is complex: while homozygous *Lhx3* inactivation in mice is lethal, heterozygous inactivation does not lead to any particular phenotype. In contrast, in humans, all described *LHX3* mutations were homozygous, and even if the phenotype was complex, it was never lethal. This discrepancy might be explained by the different weight of compensatory mechanisms performed by Lhx4 in both species, but this remains highly hypothetical [57]. The role of Lhx3 during pituitary development is crucial, as it is necessary for proper expression of several other transcription factors or receptors such as Hesx1 [62], forkhead box (fox)l2, Notch2, splicing factor (SF) 1, T-box (tbx)19 (involved in corticotroph differentiation), GnRH receptor and FSHβ [63–65], and Pou1f1 [66]. In addition to its role during pituitary development, Lhx3 is involved in the development of extrapituitary structures, such as medullar motoneurons [67, 68] (which likely explains neck rotation

anomalies in humans with *LHX3* mutations) and inner ear [69, 70] (which explains hearing trouble in humans with *LHX3* mutations). In humans, 12 homozygous *LHX3* mutations have been reported [71–77]. Pituitary phenotype usually includes GH, TSH, and LH/FSH deficiencies, while ACTH deficiency is inconstant (roughly half of the cases). On MRI, pituitary aplasia or hypoplasia is observed in 60 % cases, whereas hyperplasia is observed in 30 % cases. The mechanisms for hyperplasia are unknown but may be close to the ones reported for *PROP1* mutations (detailed later in the text). As previously mentioned, extrapituitary phenotype can include abnormal head and neck rotation (70 % cases), vertebral abnormalities (50 % cases), and mild to severe hearing deficits (50 % cases).

Late-Acting Transcription Factors: The Pituitary Phenotype Is Alone

If we only focus on transcription factors with anomalies reported in CPHD, then the list is short: PROP1 and POU1F1 are the only major actors known to be involved in pure pituitary phenotype. It does not mean that the final differentiation of thyrotrophs, for instance, or their function does not require other transcription factors such as GATA2 or maybe ISL1; it only means that no mutation of these genes has been reported so far in humans. Patients with *PROP1* or *POU1F1* mutations thus present anterior pituitary hormone deficiencies (progressive or not), normal hypothalamo-pituitary morphology at MRI (regardless of the size of the pituitary gland), and no extrapituitary malformations. In such a context, *PROP1* mutations remain the most frequently reported genetic defect.

PROP1

Prop1 is a pituitary-specific paired domain transcription factor. In mice, its expression is observed from e10 to e15.5, with a peak around e12 [78]. Prop1 is necessary for proper Pou1f1 expression, leading to somato-lactotroph and thyrotroph cell differentiation [55, 79]. In mice, the phenotype is close to the one reported in humans, except for the lack of ACTH deficiency. The reason why humans might have corticotroph deficiency (seen in about 50 % of cases) remains a mystery, and the large period of appearance (from young age to 40 years old) is another intriguing fact. In humans, at least 25 *PROP1* mutations have been reported [80–101]. Homozygous or compound heterozygous *PROP1* mutations, transmitted in an autosomal recessive manner, currently represent the most frequently identified etiologies of CPHD [1, 102, 103]. Pituitary phenotype includes GH, TSH, LH/FSH, ACTH, and PRL deficiencies, diagnosed from childhood to adulthood [104]. Pituitary MRI can show transient pituitary hyperplasia and normal or hypoplastic pituitary; pituitary hyperplasia sometimes precedes spontaneous hypoplasia [82, 105–109]. A hypothesis that may

account for this phenomenon is that pituitary progenitors might not differentiate in the absence of Prop1, thus accumulating in the intermediate lobe causing hyperplasia, with apoptosis then resulting in final hypoplasia [110].

PIT-1/POU1F 1

Pit-1 was the first pituitary-specific transcription factor identified in *Snell* mice and then in humans (POU1F1, human ortholog of Pit-1) [111]. Pou1f1 expression is first observed at e13.5 during pituitary development. Pou1f1 is necessary for thyrotroph, somatotroph, and lactotroph differentiation and remains expressed in these cell lineages at adult age. In humans, *POU1F1* mutations can be transmitted as an autosomal recessive or dominant trait. Complete TSH and GH deficiencies are usually observed during childhood, whereas gonadotroph and corticotroph axes remain functional. Brain MRI can be normal or show pituitary hypoplasia.

Conclusions and Perspectives

The identification of almost all genes identified to date in CPHD was based on the murine model. Even if it is clear that having a close animal model is crucial, the discrepancy between mice and humans might explain why only 10 % of the etiologies of CPHD have been identified today. This is an issue, as identifying the etiologies of congenital hypopituitarism is of major importance to better diagnose and treat the patients, in particular in the differential diagnosis of a pituitary mass on MRI, or to identify the patients at risk of developing delayed corticotroph deficiency and as a prenatal diagnosis to decrease the risk of early death (undiagnosed corticotroph deficiency, for instance).

Another possibility to explain this poor rate of identification is the limits in the detection techniques that we have: classical Sanger sequencing has, for instance, inherent limits with the impossibility to identify large deletions or insertions or intronic alterations leading to splicing anomalies. The development of new techniques in the recent years should dramatically improve the rate of identification of etiologies of congenital hypopituitarism: array comparative genomic hybridization (aCGH) has been created for identifying segmental genomic copy number variations (gain or loss) such as structural rearrangements (deletions, duplications, insertions, translocations) or complex chromosomal aneuploidies; it can be designed in a whole genome approach, where the array targets are equally spaced with coverage of 100 to 1000 kb. Another promising approach is whole-exome sequencing, which is based on the assumption that 85 % of mutations are located in coding regions of the genome. This technique should be of great interest in highly penetrant Mendelian diseases. However, reporting new variants in a single patient does not mean pathogenicity and requires confirmation by a similar finding in other persons presenting

with similar phenotypes. Moreover, confirmatory steps by bioinformatics analysis after a usually large dataset of results can be highly challenging.

To summarize, in one sentence, huge progress has been made over the last 20 years, but we are only at the beginning of the path. Thinking differently might likely help explaining the majority of yet unknown causes of CPHD.

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