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REVIEW

Combined pituitary hormone deficiency: current and future status

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Abstract Over the last two decades, the understanding of the mechanisms involved in pituitary ontogenesis has largely increased. Since the first description of *POU1F1* human mutations responsible for a well-defined phenotype without extra-pituitary malformation, several other genetic defects of transcription factors have been reported with variable degrees of phenotype–genotype correlations. However, to date, despite the identification of an increased number of genetic causes of isolated or multiple pituitary deficiencies, the etiology of most (80–90 %) congenital cases of hypopituitarism remains unsolved. Identifying new etiologies is of importance as a post-natal diagnosis to better diagnose and treat the patients (delayed pituitary deficiencies, differential diagnosis of a pituitary mass on MRI, etc.), and as a prenatal diagnosis to decrease the risk of early death (undiagnosed corticotroph deficiency for instance). The aim of this review is to summarize the main etiologies and phenotypes of combined pituitary hormone deficiencies, associated or not with extra-pituitary anomalies, and to suggest how the identification of such etiologies could be improved in the near future.

Keywords Pituitary development · Somatotroph deficiency · Corticotroph deficiency · Thyrotroph deficiency · Gonadotroph deficiency · Transcription factor · Hypothalamus

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Introduction

Over the last two decades, the understanding of the mechanisms involved in pituitary ontogenesis has largely increased. Since the first description of *POU1F1* human mutations responsible for a well-defined phenotype without extra-pituitary malformation, several other genetic defects of transcription factors have been reported with variable degrees of phenotype–genotype correlations (Table 1).

Two categories of patients with congenital hypopituitarism can be defined (1):

- The first group harbors a complex phenotype including anterior pituitary hormone deficiencies in association with extra-pituitary abnormalities or malformations on MRI such as pituitary stalk interruption syndrome or midline defects. The transcription factors genes involved in these phenotypes are early expressed in

Table 1 Summary of the main phenotypic characteristics of patients carrying mutations of genes coding for transcription factors (alphabetical order)

Transcription factor	Transmission	Phenotype*
ARNT2	R	Eye anomalies; inconstant pituitary deficiencies and diabetes insipidus; renal anomalies
HESX1	D/R	GH deficiency, inconstant pituitary deficiencies; pituitary hypoplasia; optic nerve anomalies, septo-optic dysplasia; ectopic posterior pituitary, corpus callosum hypoplasia
LHX3	R	GH, TSH, LH/FSH deficiencies, inconstant ACTH deficiency; pituitary hypo- or hyperplasia;. Head and neck rotation anomalies, vertebral anomalies, hearing deficits
LHX4	D	GH deficiency, inconstant pituitary deficiencies; pituitary hypoplasia, ectopic posterior pituitary; Chiari syndrome, corpus callosum hypoplasia
OTX2	D	GH deficiency, inconstant pituitary deficiencies; pituitary hypoplasia; ectopic posterior pituitary, Chiari syndrome
PITX2	D/R	Axenfeld–Rieger syndrome; inconstant pituitary deficiencies
POU1F1	D/R	GH, TSH, prolactin deficiencies; pituitary hypoplasia
PROP1	R	GH, TSH, LH/FSH deficiencies, inconstant ACTH deficiency; pituitary hypo- or hyperplasia
SOX2	R	Gonadotroph deficiency, inconstant GH, TSH, ACTH deficiencies; pituitary hypoplasia; microphthalmia; mental retardation
SOX3	X-linked	Mental retardation, GH deficiency or panhypopituitarism and brain anomalies

Please note that the signs described in this table are not always constant

D dominant, *R* recessive

regions that determine the formation of forebrain and related midline structures such as the hypothalamus and pituitary. Mutations in these genes are therefore characterized by marked phenotypic heterogeneity.

- The second group corresponds to a "pure" endocrine phenotype including anterior pituitary hormone deficiencies (progressive or not), normal hypothalamo-pituitary morphology at MRI (regardless of the size of the pituitary gland) and no extra-pituitary malformation. These phenotypes are due to mutations of late-acting pituitary-specific transcription factors. In such a context, PROP1 gene mutations remain the most frequently reported genetic defect.

Despite identification of an increased number of genetic causes of isolated or multiple pituitary deficiencies, the etiology of most congenital cases of hypopituitarism remains unsolved. The aim of this review is to summarize the main etiologies and phenotypes of combined pituitary hormone deficiencies, associated or not with extra-pituitary anomalies, and to suggest how the identification of such etiologies could be improved in the near future. We will not detail in this review the etiologies of isolated pituitary deficiency (somatotroph, thyrotroph, corticotroph or gonadotroph).

Brief overview of pituitary development (based on murine models)

Human pituitary development is close to murine pituitary development, which thus represents an appropriate model to determine the major temporo-spatial interactions between signaling pathways and transcription factors leading to a mature endocrine organ [1, 2]. Pituitary ontogenesis begins early during brain neurogenesis, around embryonic day (e) 7.5, corresponding to the first visualization of the pituitary placode [3]. 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. 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 SOX2, SOX9, ISL-1… [5–7]. This first step leading to terminal differentiation of the pituitary is possible due to a tightly controlled temporo-spatial gradient of morphogenic factors from different origins, the diencephalon (BMP4, FGF8, 10 et 18, Wnt5a), the ectoderm (*Isl1*, BMP2, *Sonic Hedgehog (Shh)*, Wnt 4), the ventral mesoderm (Chordin, BMP2) [8], or the pituitary cells. At e11.5, αsubunit is expressed in the rostral tip [9], followed by ACTH (e12.5), TSHβ (e14.5), Pomc (e14.5, intermediate lobe), GH and prolactin (e15.5) [10], Lhβ (e16.5), and finally Fshβ (e17.5). Precise mechanisms leading to this differentiation and the formation of pituitary cell networks remain incompletely understood. Pituitary-

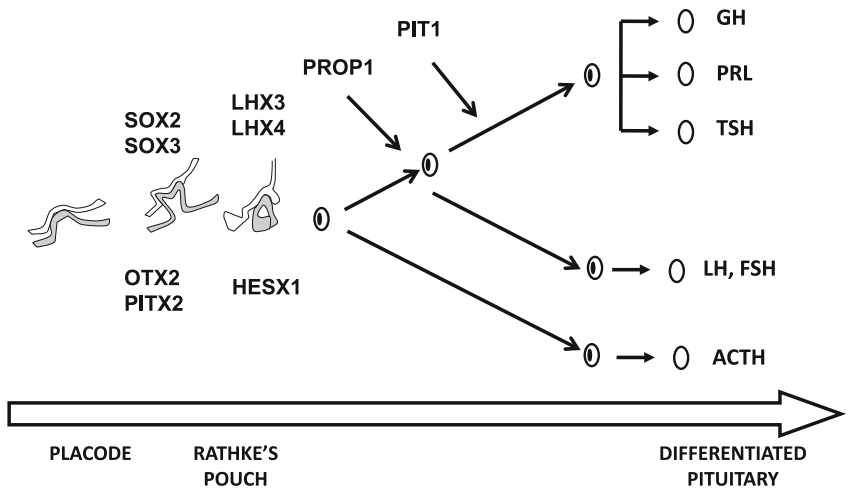

Fig. 1 Simplified scheme representing the main transcription factors expression during pituitary development. Note that early transcription factors dysfunction is associated with pituitary and extra-pituitary anomalies, whereas late transcription factors (PIT1, PROP1) dysfunction is associated with pure pituitary phenotype

specific or non-specific transcription factors are involved in a timely manner during these steps of differentiation, early acting such as Lhx3, Lhx4, Pitx2, Hesx1 or ARNT2 [11], or late-acting such as Prop1 and Pou1f1. Early acting transcription factors are also involved in the development of other organs (eye, inner ear, etc.), and their defects lead to extra-pituitary anomalies, whereas alterations of late-acting transcription factors usually lead to a pure pituitary phenotype, as previously mentioned (Fig. 1).

Congenital hypopituitarism and extra-pituitary anomalies

Pituitary deficiency and midline anomalies (holoprosencephaly, septo-optic dysplasia and pituitary stalk interruption syndrome)

Midline anomalies include a wide range of phenotypic signs, from cleft palate and pituitary stalk interruption syndrome, to septo-optic dysplasia or holoprosencephaly. 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]. It has long been considered as a post-natal trauma consequence; however, the fact that only 30 % of patients had a history of such an event, and existence of familial cases led to searching for genetic etiologies. Septo-optic dysplasia is defined by the association of brain anomalies (septum agenesis or corpus callosum agenesis), optic nerve hypoplasia and pituitary deficiencies (at least two of these characteristics) [13]. Holoprosencephaly is a complex brain malformation, affecting both brain and face, due to an abnormal division of the prosencephalon between days 18 and 28. Facial anomalies include cyclopia, median or bilateral labial and/or palatal cleft, hypotelorism or a single median incisor in milder. Mental retardation is frequently associated. Several distinct genes defects have been associated with such anomalies (*SHH, ZIC2, SIX3, TGIF, HESX1, SOX2, SOX3, OTX2*, etc.). However, recent studies emphasized 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].

Sonic-hedgehog pathway (gli2)

Sonic-hedgehog (SHH) signaling pathway and its targets, GLI transcription factors, is involved in the early steps of pituitary development. *SHH* mutations have been reported in patients with holoprosencephaly [17]. *GLI2* heterozygous mutations have also been reported in patients with holoprosencephaly, or with pituitary hormone deficits and less severe cranio-facial anomalies such as polydactyly, and pituitary hypoplasia, corpus callosum agenesis or ectopic posterior pituitary on brain MRI.

Hesx1

Hesx1 expression has been observed very early in the pituitary placode. Its expression is restricted to Rathke's pouch at e8.5–e9. Decreased expression at e13 is necessary for PROP1 and secondarily Pou1f1 expression, leading to differentiation of GH-, TSH- and PRL-secreting cells [18–21]. Other transcription factors are also necessary for proper HESX1 expression, such as LIM domain Lhx1 and Lhx3, or Six3 transcription factors [22]. In humans, 16 *HESX1* mutations have been reported [18, 23–31]. Patients with homozygous mutations (40 % cases) usually presented a more severe phenotype than the ones with heterozygous mutations [32]. Pituitary phenotype includes GH deficiency in all patients, whereas other pituitary

deficiencies are only observed in 50 % cases. Optic nerve anomalies are the other major phenotypic sign, observed in 30 % cases. In contrast, only 1 % of septo-optic dysplasia cases have been linked to HESX1 mutations [32–34] [35]. Brain MRI usually reveals a pituitary hypoplasia (80 % cases); extra-pituitary anomalies include ectopic or non-visible posterior pituitary in 50–60 % cases, and corpus callosum agenesis or hypoplasia in 25 % cases.

Fgf8 et fgfr1

The expression of FGF8 and FGFR1 in the ventral diencephalon is necessary for proper Rathke's pouch formation and temporo-spatial pattern of pituitary cell lineages. FGF8 overexpression stimulates melanotroph and corticotroph lineages, and inhibits gonadotroph, somatotroph, thyrotroph and lactotroph [36]. ***FGFR1*** **and** ***FGF8*** heterozygous mutations have first been reported in 10 % of Kallmann syndrome and 7 % of normosmic hypogonadism [37]. Penetrance was incomplete [38, 39]. Pituitary MRI showed normal or hypoplastic anterior pituitary and inconstant ectopic posterior pituitary. Other anomalies were reported such as ear hypoplasia, dental agenesis, cleft palate and distal limb malformations. FGFR1 and FGF8 mutations have also been reported in patients with septo-optic dysplasia, with about 4 % prevalence [14].

Prokineticin pathway: PROK2 and PROKR2

Prokineticin pathway is known to be involved in portal angiogenesis and neuronal development and migration [40]. Involvement of the prokineticin pathway has thus been suggested as a possible cause of pituitary stalk interruption syndrome. ***PROK2*** **and** ***PROKR2*** mutations have been recently reported in a cohort of patients with pituitary deficiencies, anterior pituitary hypoplasia or aplasia, and stalk interruption syndrome [15]. These results have been also reported thereafter in patients with septo-optic dysplasia, and inconstant additional brain abnormalities, such as cerebellar hypoplasia, Dandy–Walker cyst, focal abnormality of mesial frontal cortex have also been reported on brain MRI [16]. However, the prevalence of mutations in PSIS or SOD is estimated to be below 3 %.

Pituitary deficiency and eye anomalies

Otx2

Otx2 is a paired homeodomain transcription factor involved in the early steps of brain development. 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 GnRH neurons development [41]. In humans, 25 heterozygous de novo *OTX2* mutations have been reported, including 9 in patients with congenital hypopituitarism; the remaining 16 mutations were reported in patients with ophthalmic diseases, and no mention of pituitary axes evaluation [42–46]. All but one mutation induced a loss of function, the last being responsible for a dominant negative effect. Phenotype is highly variable in terms of pituitary deficiencies (from isolated GH deficiency to panhypopituitarism) and of brain MRI (normal or hypoplastic pituitary, inconstant ectopic posterior pituitary and Chiari syndrome).

Sox2

Sox2 is an "HMG DNA binding domain" transcription factor. At e 9.5, 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 lateral ventricles and in the dentate gyrus. In humans, heterozygous de novo *SOX2* mutations have been observed in six patients with hypogonadotroph hypogonadism, bilateral microphthalmia, corpus callosum hypoplasia and inconstant mental retardation. Pituitary phenotypes included inconstant GH, TSH or ACTH deficiencies, pituitary hypoplasia in 80 % cases, and ectopic posterior pituitary. Extra-pituitary anomalies including corpus callosum anomaly has been reported in 1 case [47].

Pitx2

PITX2 is a paired homeodomain transcription factor expressed in the stomodeum at e8, Rathke's pouch at e10.5 [48, 49], and pituitary anterior and intermediate lobes at e12.5. At adult age, PITX2 is expressed in thyrotrophs and gonadotrophs [50]. Pitx2 expression is ubiquitous, as it has also been observed in adult brain, eye, kidney, lungs, testis and tongue [48, 51]. 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 (cranio-facial dysmorphy, dental, and umbilical anomalies) [52, 53]. Pituitary phenotype is rare, with only three patients reported with GH deficiency and pituitary hypoplasia [54–56]. Abnormal pituitary shape has also been described on MRI [57]. PITX2 is not the only transcription factor involved in this syndrome, as mutations of *FOXC1*, a forkhead homeodomain transcription factor, have also been reported.

Arnt2

A complex syndrome of post-retinal eye abnormalities, congenital hypopituitarism with diabetes insipidus, renal and central nervous system anomalies has recently been described [11] in a large consanguineous kindred. It was shown to be related to a defect in the Helix-Loop-Helix transcription factor ARNT2 that plays a critical role in the development of hypothalamus and other CNS structures as well as kidneys or eyes. Brain MRI was similar for all patients, with absent posterior pituitary bright spot, thin pituitary stalk, hypoplastic anterior pituitary, hypoplastic frontal and temporal lobes, thin corpus callosum and delay in brain myelination [11].

Pituitary deficiency and mental retardation

Mental retardation can be associated with early neurogenesis anomalies (including septo-optic dysplasia or holoprosencephaly). A male predominance has been observed, leading to a search for X-linked transcription factors [58]. In humans, X transmitted *SOX3* mutations have been associated with either mental retardation and GH deficiency [59], or panhypopituitarism and brain anomalies (corpus callosum hypoplasia, hypoplastic or non-visible stalk, ectopic posterior pituitary) [60]. A lack of strict intrafamilial genotype–phenotype correlation was reported [61].

Pituitary deficiency and intermediate neurogenesis anomalies

Lhx4

LHX4 is a LIM domain transcription factor, involved in the early steps of pituitary development. 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 [62, 63]. In humans, 11 sporadic or familial *LHX4* mutations have been reported in 17 patients [64], with a wide intra- and inter-familial phenotypic variability in terms of pituitary phenotype (ranging from isolated GH deficiency to complete panhypopituitarism) [65, 66] and brain MRI (pituitary hypoplasia, inconstant ectopic posterior pituitary and sellar hypoplasia, corpus callosum hypoplasia or Chiari syndrome). Of note, one patient carrying 1q25 microdeletion (including *LHX4* deletion) was also presenting with heart defect. In our cohort of patients with pituitary stalk interruption syndrome, *LHX4* mutations have been observed in 2.4 % cases [58].

Lhx3

Lhx3 is another LIM domain transcription factor, with a similar pituitary expression profile as Lhx4. Both factors seem to have redundant roles during pituitary development, and proper Lhx3 expression requires Lhx4, as LhxX3 is not observed at e12.5 in mice with homozygous inactivation of *Lhx4*; however, the fact that Lhx3 expression is reported in these mice at e14.5 suggest that there are compensatory mechanisms (likely PROP1) allowing delayed expression of Lhx3 [62]. Lhx3 is involved in extra-pituitary structures development, such as medullar motoneurons [67, 68], and inner ear [69, 70]. Lhx3 is also necessary for proper expression of Hesx1 [71], foxl2, Notch2, SF1, tbx19 (involved in corticotroph differentiation), GnRH receptor and FSHβ [72–74] and Pou1f1. Lhx3 interacts with Pou1f1 for promoting prolactin, and TSHβ genes expression [75]. In humans, 12 homozygous *LHX3* mutations have been reported [76–82]. All but one (*p.K50X*) were familial [82]. Pituitary phenotype usually includes GH, TSH and LH/FSH deficiencies. ACTH deficiency is inconstant, reported in 58 % of the mutations. On MRI, pituitary aplasia or hypoplasia is observed in 60 % cases, whereas hyperplasia is observed in 30 % cases. Pituitary MRI is considered normal in 10 % cases. Of note, one patient was presenting with an MRI suggesting a microadenoma. Extra-pituitary phenotype can include abnormal head and neck rotation (70 % cases), vertebral abnormalities (50 % cases), and mild-to-severe hearing deficits (50 % cases).

Purely endocrine combined pituitary phenotype

Prop1

Prop1 is a pituitary-specific paired domain transcription factor. Its expression is observed from e10 to e15.5, with a peak around e12 [83]. Prop1 is likely involved in pituitary progenitors differentiation, by interacting with Notch [5, 7, 84], and is necessary for proper Pou1f1 expression, leading to somato-lactotroph and thyrotroph cells differentiation [85]. In humans, at least 25 *PROP1* mutations have been reported [86–107]. Homozygous or compound heterozygous *PROP1* mutations, transmitted in an autosomal recessive way, currently represent the most frequently identified etiologies of CPHD [1, 108, 109]. Pituitary phenotype includes GH, TSH, LH/FSH, ACTH and PRL deficiencies, diagnosed from childhood to adulthood [110]. *W194X* mutation, the first one mutation in the transactivation domain [92], led to an unusual phenotype, with initial isolated gonadotroph deficiency, and delayed GH deficiency in two of the three patients of the family. Interestingly, the other mutation (*S156InsT*) located in the transactivation domain, led to a classical phenotype [89]. Corticotroph deficiency, present in 50 % cases, is surprising, as mice with spontaneous *Prop1* inactivation, have normal ACTH secretion. The precise mechanisms leading

to this usually delayed phenotype, by up to 35–40 years [111], remain unknown [96, 112]. Pituitary MRI can show transient pituitary hyperplasia, normal or hypoplastic pituitary: pituitary hyperplasia sometimes precedes spontaneous hypoplasia [88, 113–117]: an hypothesis that may account for this phenomenon is that pituitary progenitors would not differentiate in the absence of Prop1, accumulate in the intermediate lobe (hyperplasia), and secondary present apoptosis (final hypoplasia) [118]. No extra-pituitary anomaly has been reported to date.

Pit1/POU1F1

Pit1 was the first pituitary-specific transcription factor identified in *Snell* mice and then in humans (POU1F1, human ortholog of Pit1) [119]. 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. Pou1f1 requires Prop1 expression [120–124], and is able to interact with other transcription factors such as Lhx3 (prolactin promoter) and Gata2 (TSHβ promoter) [79, 125], ubiquitous proteins (CBP), or protein complexes such as med/Trapp220 [126]. 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 shows pituitary hypoplasia. No extra-pituitary anomaly has been reported to date.

Perspectives: looking for etiologies and new genes

Classical approach and sequencing algorithm

Almost all the genes reported to date as being involved in CPHD have been discovered via a murine model and extrapolation on human phenotypes. Though this approach allowed the discovery of several genes, it is limited by differences between both species: for instance, as previously mentioned, corticotroph axis is always normal in *Ames* mice, whereas corticotroph deficiency is reported in roughly 40 % of human cases with *PROP1* mutations. This likely explains, at least in part, why only 10 % of CPHD etiologies have been identified to date. Based on phenotypes described in the literature and our experience in the Genhypopit network, we defined an algorithm allowing the clinician and the geneticist to look for the most appropriate genes to sequence when a congenital hypopituitarism is diagnosed (Fig. 2). Recent data, however, suggest that alterations of some genes initially thought to be involved in a specific phenotype, can actually lead to a wider range of phenotypes. This algorithm thus has to be frequently updated by including novel genes and/or phenotypes.

Classical Sanger sequencing has inherent limits with the impossibility to identify large deletions or insertions, or intronic alterations leading to splicing anomalies. Recent years allowed the development of new techniques, which should dramatically improve the rate of identification of etiologies of congenital hypopituitarism.

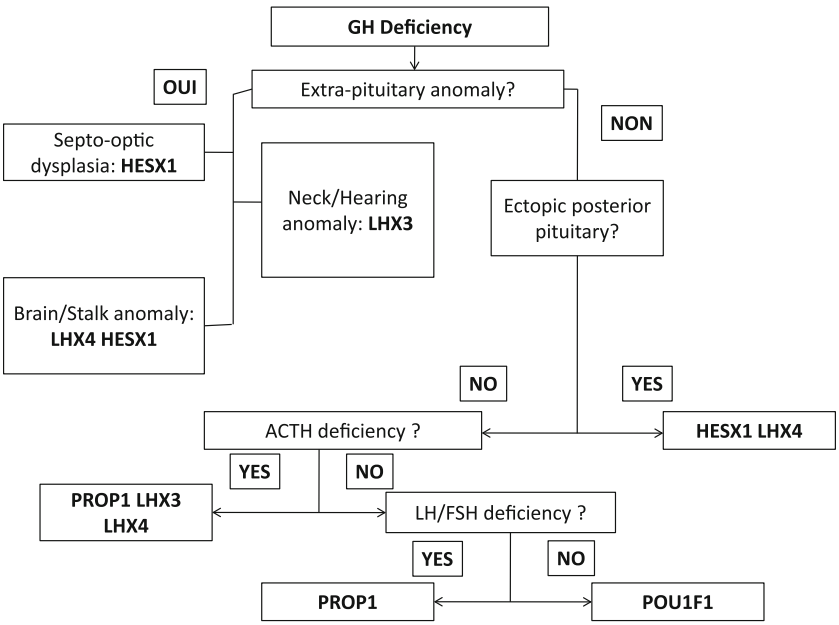

Fig. 2 Simplified sequencing algorithm for patients with congenital hypopituitarism

Modern approaches

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. In contrast with fluorescent in situ hybridization (FISH), which requires a previous knowledge of the zone of interest, aCGH can also be used to identify new genes involved in monogenic disorders: first, large deletions can include new genes involved in a specific phenotype; aCGH can be designed in a whole genome approach, where the array targets are equally spaced with coverage of 100–1,000 kb. Main limitations is the impossibility to detect balanced translocations, and for the whole genome approach, the risk of "over-detection", i.e., detecting numbers of rearrangements of low or undetermined clinical significance.

Another 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. Confirmatory steps by bioinformatics analysis after a usually large dataset of results can thus be highly challenging. In contrast, identifying variants known to be involved in other unrelated diseases raises ethical questions for patients and offspring.

Conclusions

Identifying the etiologies of congenital hypopituitarism is of major importance

- As a post-natal diagnosis 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.
- As a prenatal diagnosis to decrease the risk of early death (undiagnosed corticotroph deficiency for instance).

Classical candidate gene approach has shown some limits in detecting new etiologies of congenital hypopituitarism mainly because it was based on murine models not always concordant with human diseases. New pangenomic approaches have also their own limits, the first of which currently being their cost, the second the difficulties in interpreting and filtering the large dataset of results obtained. However, combining all of these techniques should allow increasing the currently low rate (about 10 %) of identified etiologies of congenital hypopituitarism in the next few years.

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Conflict of interest None.

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