Chapter 2
Genetics of Hypopituitarism

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Key Points

- Coordinated temporal and spatial expression of numerous transcription factors is essential for normal pituitary gland development and function.
- The pituitary gland is responsible for the production of hormones that play a crucial role in growth, metabolism, puberty and reproduction, lactation, and stress response.
- Several mutations in patients with hypopituitarism have been identified; however, the vast majority of patients remain labeled idiopathic.
- Next-generation sequencing technology is expanding our understanding of the underlying genetic mechanisms of hypopituitarism and has the potential of revolutionizing clinical care.

Case Presentation

A 5-year and 3-month-old boy was referred to the pediatric endocrinology clinic for evaluation of short stature. Other than his height, his parents did not have any concerns and reported him to be a healthy child. His birth history was normal with a weight of 3.4 kg and length of 49 cm, without a history of jaundice or hypoglycemia. His height measurement was 94 cm (−3.6 SDS) with a midparental target

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height of 178 cm, and weight was 14 kg (−0.17 SDS), resulting in a BMI of 15.84 kg/m2 (63rd percentile). A review of his growth charts from the pediatrician showed a poor growth velocity since birth. On exam, he had an absence of dysmorphic features or midline defects and normal-appearing external male genitalia without a micropenis. His initial screening laboratory studies revealed a normal complete blood count (CBC), complete metabolic panel (CMP), thyroid-stimulating hormone (TSH), celiac panel, and urine analysis; however, low levels of serum insulin-like growth factor 1 (IGF-1) and insulin-like growth factor-binding protein 3 (IGF-BP3)) were seen. His bone age X-ray showed delayed skeletal maturation. Growth hormone stimulation testing with arginine and clonidine revealed subnormal growth hormone levels with a peak level less than 5 ng/mL. MRI imaging revealed a hypoplastic anterior pituitary with a normally positioned stalk and posterior bright spot. In light of the imaging, further laboratory workup was ordered, which revealed a low free T4 level of 0.6 ng/dL, with an inappropriately normal TSH of 1.8 μIU/mL, and a low prolactin level. No other pituitary abnormalities were found with appropriately prepubertal gonadotropin levels and a normal AM cortisol level of 15.2 μg/dL. The patient was started on injections of recombinant growth hormone at a dose of 0.6 mg daily as well as levothyroxine orally, resulting in a significant improvement in growth velocity.

Introduction and Clinical Presentation of Hormone Deficiencies

The pituitary gland lies in the hypophyseal fossa, the deepest part of the sella turcica, located in the sphenoid bone of the neurocranium. It is comprised of two distinct structures, the adenohypophysis (anterior and intermediate lobes) and neurohypophysis (posterior lobe), which differ in embryologic origin. The anterior originates from Rathke's pouch, an invagination of the oral ectoderm, while the posterior lobe arises from the neuroectoderm. Numerous transcription factors act in a coordinated temporal and spatial sequence during pituitary development and ultimately result in the differentiation of specific pituitary cell lineages. The anterior lobe has five distinct cell types that produce six hormones: somatotrophs (growth hormone [GH]), thyrotrophs (thyrotropin also known as thyroid-stimulating hormone, [TSH]), gonadotrophs (luteinizing hormone [LH] and follicle-stimulating hormone, [FSH]), lactotrophs (prolactin), and corticotrophs (adrenocorticotropin, [ACTH]). These hormones play a crucial role in growth, metabolism, puberty and reproduction, lactation, and stress response.

Combined pituitary hormone deficiency (CPHD), defined as the deficiency of more than one anterior pituitary hormone, is associated with severe morbidity and can be life-threatening. The clinical presentation varies depending on age as well as the number and severity of hormone deficiencies. Many findings are non-specific, especially in the newborn period, mandating a high index of suspicion, particularly in patients with midline defects.

Newborns with growth hormone deficiency (GHD) may not show overt growth failure and, however, may present with hypoglycemia and prolonged jaundice. When combined with gonadotropin deficiency, genitourinary abnormalities such as microphallus and cryptorchidism can be seen. Children present with growth failure evidenced by poor growth velocity, short stature, and an increased weight-to-height ratio. Pulsatile secretion and the short half-life of GH limit the use of random serum GH levels. However, IGF-1, the primary mediator of the actions of GH, and its most abundant carrier protein, IGF-BP3, are stable throughout the day and therefore useful screening labs. Growth hormone stimulation testing, although imperfect, [1] can be performed using several protocols [2] and can aid in establishing the diagnosis of GHD. Recombinant growth hormone is the treatment of choice and is commonly administered once daily via subcutaneous injections.

Although congenital hypothyroidism (CH) due to TSH deficiency is rare, early diagnosis and treatment are critical to prevent adverse neurological outcomes [3]. Infants can present with myxedema, hypotonia, hoarse cry, poor feeding, macroglossia, umbilical hernia, large fontanels, hypothermia, and prolonged jaundice. Some symptoms overlap with those seen in childhood such as lethargy, constipation, and dry skin. Additional features seen in children include poor linear growth, cold intolerance, brittle hair, and a decline in academic performance. Newborn screening protocols for CH vary by state, and central hypothyroidism can be missed with primary TSH with backup thyroxine (T4) measurements [3]. If suspected, free or total T4 should be assessed since TSH can be inappropriately normal. Levothyroxine (synthetic form of T4) is the treatment of choice.

Hypogonadotropic hypogonadism resulting from deficient secretion of LH and FSH can lead to genitourinary abnormalities as discussed above in boys; however, the prevalence of these findings at birth is low, suggesting maternal hCG has an important role in fetal testosterone production. Newborn girls have normal-appearing external genitalia. Within the first few months of life, infants experience a transient activation of the hypothalamic-pituitary-gonadal axis. This process, sometimes referred to as "mini-puberty," leads to penile and testicular growth in males and maturation of ovarian follicles in females; however, the biological relevance remains unclear [4]. Low gonadotropin and sex steroid levels during this brief window can lead to early identification of congenital hypogonadotropic hypogonadism. Failure to undergo pubertal development with its associated growth spurt is seen later in childhood and adolescence and is the most common presentation of isolated hypogonadotropic hypogonadism. Prepubertal serum concentrations of sex steroid hormones along with low or "normal" serum LH and FSH concentrations are seen. A prepubertal biochemical profile is also seen in constitutional delay of growth and puberty, making the distinction between these two conditions challenging. Sex steroid treatment goals include attainment of secondary sex characteristics, normal growth spurt, and fertility preservation.

The main physiologic role of prolactin is for lactation. Isolated prolactin deficiency is rare, and therefore identified patients often have manifestations of other pituitary hormone deficiencies [5].

ACTH deficiency (secondary adrenal insufficiency) results in cortisol deficiency, the primary glucocorticoid secreted by the adrenal cortex. Cortisol is essential for stress response and has significant effects on carbohydrate, protein, and fat metabolism as well as anti-inflammatory effects. Generally, the presentation of anterior pituitary hormone deficiencies is similar to primary deficiencies of the target organs they control; however, there are two distinct differences between primary and secondary adrenal insufficiency. ACTH deficiency does not lead to mineralocorticoid deficiency, as this pathway is primarily regulated by the renin-angiotensin-aldosterone system, and therefore does not result in salt wasting, hyperkalemia, and volume contraction. However, hyponatremia can be seen in secondary adrenal insufficiency due to inappropriate secretion of vasopressin [6]. Second, ACTH deficiency is not associated with hyperpigmentation, which results from high circulating ACTH and other melanocyte-stimulating hormone levels. Initial laboratory studies should include cortisol (measured around 8 am once diurnal patterns are established) and ACTH levels. Low-dose (1 μg) cortrosyn (synthetic ACTH) stimulation testing can aid in confirming the diagnosis. In an adrenal crisis, emergency treatment is crucial, starting with fluid resuscitation, intravenous glucose, and parenteral glucocorticoid treatment. Chronic treatment may require oral glucocorticoid replacement at physiologic doses, typically lower compared to treatment of primary adrenal failure, with stress dosing as needed. Clinical status, weight gain, and growth velocity need to be monitored closely to avoid overtreatment. Patients with partial ACTH deficiency may only need glucocorticoid treatment at times of increased physiologic stress.

PROP1

Prophet of Pit-1 (Prop1) is a pituitary-specific transcription factor that plays a critical role in the differentiation of somatotrophs, lactotrophs, thyrotrophs, and gonadotrophs. The human PROP1 gene, located at chromosomal position 5q35, has at least 3 exons encoding 226 amino acid proteins and spans less than 4 kb of genomic DNA. It contains both a paired-like DNA-binding protein and a C-terminal transactivation domain [7].

Mutations in the PROP1 gene are the most frequent genetic defects identified in patients with CPHD [8]. In a study of 10 unrelated CPHD kindreds, 55% (11 of 20) of the PROP1 alleles had the 301-302delAG deletion in exon 2. The same study evaluated 21 sporadic cases of CPHD, and although only 12% of the PROP1 alleles were 301delAG, when the sporadic cases were subdivided into a multiple hypopituitary group and a multiple hypothalamic group based on TRH stimulation testing, the frequency increased to 50% in the hypopituitary group [8]. Analysis of a tightly linked polymorphic marker, D5S408, led the authors to conclude that these deletions may be independent recurring mutations rather than being inherited from a single common founder mutation [8]. A later study of 73 individuals with CPHD found that 35 patients had PROP1 gene defects, including 3 missense

mutations, 2 frameshift mutations, and 1 splice site mutation [9]. Three tandem repeats of the dinucleotides GA at location 296–302 were identified as a hot spot [9]. Mutations typically involve the DNA-binding homeodomain; however, a mutation affecting the transactivating domain resulting in a truncated protein with only 34% activity of that of the wild-type PROP1 has been reported, suggesting a critical functional role of the C-terminal end of the transcription factor in protein-DNA interaction [10].

Studies on the Ames dwarf (df) mouse, which harbors a missense mutation in the Prop1 gene, leading to attenuated DNA-binding and transactivation capacity, show that Prop1 messenger RNA (mRNA) is expressed in the developing pituitary gland before Pit-1 mRNA expression, with maximal expression by e12.0 [11]. Prop1 plays a critical role in the expression of Pit1 and the development of Pit1-dependent cell lineages (somatotroph, lactotroph, and thyrotroph) in early pituitary organogenesis [11]. PROP1 involvement in gonadotropin and ACTH deficiencies has been explored; however, the mechanisms remain unclear [12].

The first reports of humans with CPHD due to mutations of the PROP1 gene found that in contrast to individuals with POU1F1 mutations, gonadotropin deficiency is present and therefore affected individuals do not enter puberty spontaneously, suggesting a direct or indirect role for PROP1 in gonadotroph ontogenesis [13]. Interestingly, isolated hypogonadotropic hypogonadism was the initial presentation in three brothers from a consanguineous family found to be homozygous for a nonsense mutation (W194X) in the PROP1 gene [14].

A retrospective analysis of nine CPHD patients with known PROP1 mutations found that all patients developed progressive decline with age in anterior pituitary function, including adrenal insufficiency. All patients developed at least partial adrenal insufficiency and eventually needed hydrocortisone replacement at a mean age of 18.4 +/− 3.5 years [15]. Further, evaluation of a large consanguineous Indian CPHD pedigree with homozygosity for a 13-bp deletion in exon 2 predicted to generate a null allele revealed severe cortisol deficiency in two patients. These data suggest a role for PROP1 in the differentiation and/or maintenance of corticotroph cells and highlight that the impairment of the pituitary-adrenal axis in CPHD patients does not exclude an underlying PROP1 gene defect [16].

Phenotypic variability, even among patients with the same mutation, has been described. A study of five patients with CPHD, homozygous for the R120C mutation, showed that each patient followed a different pattern and time scale in the development of pituitary hormone deficiencies; the age at diagnosis was dependent on the severity of symptoms. Although all five patients eventually presented with gonadotropin deficiency, they all entered puberty, and two females experienced menarche [17]. The most consistent feature is short stature; however, normal growth and attainment of normal adult height have been reported [10, 18]. One such patient was a female with expected hypogonadotropic hypogonadism, who continued to grow until age 20 years at which time she reached a normal adult height. The lack of circulating estrogen delaying epiphyseal fusion and resulting in a prolonged period of growth was noted among the contributing factors [18].

Magnetic resonance imaging (MRI) of the brain in most patients showed some degree of anterior pituitary hypoplasia with a normal-appearing stalk and posterior pituitary; however, normal and even pituitary enlargement has been reported [19, 20]. It has also been shown that pituitary morphology can change over time in patients with PROP1 mutations. MRI imaging on an 8-year-old female with severe short stature, homozygous for the 301AG deletion, initially showed pituitary gland enlargement (8 mm in height). Repeat imaging at age 15 years showed a significantly reduced pituitary height of 2 mm [20].

POU1F1 (PIT1)

POU1F1 (also known as PIT1) is pituitary-specific transcription factor essential for the development of the somatotroph, lactotroph, and thyrotroph cell lineages [21]. It is a founding member of the POU family of transcription factors, characterized by two protein domains, the POU-homeodomain and the POU-specific domain, both necessary for high-affinity DNA binding [21]. The human POU1F1 gene is located on chromosome 3p11 and contains six exons [22].

Most patients are homozygous for a recessive mutation or have a dominant negative mutation in codon 271, a well-recognized hot spot [23]; however, compound heterozygosity has also been described [24, 25]. An additional hot spot, E230K, has been suggested, as this mutation was identified in five different pedigrees; however, most were Maltese, bringing into question a founder effect [23]. A recent study explored the underlying molecular mechanisms of Pit1-mediated gene activation and found that the R271W mutation results in loss of Pit1 association with beta-catenin and SATB1. This association is required for binding of Pit1-occupied enhancers to a nuclear matrin-3-rich network/architecture, which is a key event in effective activation of gene transcription [26].

The first reports of POU1F1 mutations in humans were described in 1992 by four independent groups, all of which described patients with growth hormone, prolactin, and thyrotropin deficiency [27–30]. This triad of hormone deficiencies has been well described in association with POU1F1 gene mutations with the majority of patients presenting with growth failure secondary to growth hormone deficiency [24]. Wide variability with respect to thyrotropin deficiency has been described. An infant born to a mother, both heterozygous for the R271W mutation, highlighted the importance of transplacental thyroxine transfer. At birth, both the infant and mother had undetectable serum thyroxine levels, resulting in significant respiratory, cardiovascular, and neurological morbidity, as well as delayed bone maturation in the infant [31]. While this study reported severe congenital hypothyroidism, other studies have shown preservation of TSH secretion, even into the third decade of life [23]. MRI imaging in patients with POU1F1 mutations shows either a small or normal anterior pituitary, with a normal posterior pituitary [25].

Case Continued

Ongoing clinical and biochemical monitoring revealed delayed puberty secondary to hypogonadotropic hypogonadism, without associated anosmia. Genetic testing revealed a 2-bp deletion in exon 2 of the PROP1 gene.

Key Points

- POU1F1 mutations are associated with the classic triad of growth hormone, prolactin, and thyrotropin deficiency; in addition to this triad, PROP1 mutations can include gonadotropin and cortisol deficiency.
- There can be phenotypic variability in the age at presentation and severity of hormone deficiencies; therefore, monitoring for progressive pituitary decline is critical.
- MRI pituitary imaging shows either a hypoplastic or normal-sized anterior pituitary is those with POU1F1 mutations, while a hypoplastic, normal, or even enlarged anterior pituitary is seen in patients with PROP1 mutations; further pituitary morphology can change over time in patients with PROP1 gene mutations including spontaneous involution of pituitary hyperplasia.
- Despite phenotypic variability, establishing the genotype in patients with CPHD is important as it can guide clinical decision-making including predicting disease progression and avoidance of unnecessary surgery and can facilitate genetic counseling.

Future Considerations

Pituitary gland development is a complex orchestrated process that results in essential hormone production. Advances in molecular genetics have identified mutations within genes encoding pituitary transcription factors in patients with isolated or syndromic hypopituitarism, expanding our understanding of the underlying molecular basis. However, the vast majority of affected patients remain labeled as idiopathic, presumably due to mutations yet to be identified as well as modifier genes and environmental factors. Next-generation sequencing (NGS), including whole-genome sequencing (WGS) and whole-exome sequencing (WES), are now being used in clinical care [32]. The less expensive of the two, WES, provides coverage of more than 95% of exons, which contain 85% of disease-causing mutations in Mendelian disorders [33]. Ethical concerns have been raised including the assessment of significance and the need for user-friendly software in the analysis of the raw sequence [33]. Nonetheless, WES and eventually WGS hold the potential of exponentially increasing our knowledge of the genetic basis of hypopituitarism and personalizing preventive, diagnostic, and therapeutic patient care.

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