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PROP1-Related Combined Pituitary Hormone Deficiency

Synonym: *PROP1*-Related CPHD

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Summary

Clinical characteristics

PROP1-related combined pituitary hormone deficiency (CPHD) is associated with deficiencies of: growth hormone (GH); thyroid-stimulating hormone (TSH); the two gonadotropins, luteinizing hormone (LH) and follicle-stimulating hormone (FSH); prolactin (PrL); and occasionally adrenocorticotropic hormone (ACTH). At birth, in contrast to individuals with congenital CPHD of other etiologies, neonates with *PROP1*-related CPHD lack perinatal signs of hypopituitarism. Mean birth weights and lengths are usually within the normal range and neonatal hypoglycemia and prolonged neonatal jaundice are not prevalent findings.

Most affected individuals are ascertained because of short stature during childhood. Although TSH deficiency can present shortly after birth, TSH deficiency usually occurs with or after the onset of GH deficiency. Hypothyroidism is usually mild. FSH and LH deficiencies are typically identified at the age of onset of puberty. Affected individuals can have absent or delayed and incomplete secondary sexual development with infertility. Untreated males usually have a small penis and small testes. Some females experience menarche but subsequently require hormone replacement therapy. ACTH deficiency is less common and, when present, usually occurs in adolescence or adulthood. Neuroimaging of hypothalamic-pituitary region usually demonstrates a hypoplastic or normal anterior pituitary lobe and a normal posterior pituitary lobe.

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Diagnosis/testing

The diagnosis of *PROP1*-related CPHD is established in a proband with suggestive findings and biallelic pathogenic variants in *PROP1* identified by molecular genetic testing.

Management

Treatment of manifestations: GH deficiency is treated with injection of biosynthetic growth hormone. TSH deficiency is treated by thyroid hormone replacement in the form of oral L-thyroxine. In male infants with LH and FSH deficiency, micropenis is treated with a limited course of testosterone. Hormone replacement to induce secondary sex characteristics can be initiated in males at age 12 to 13 years with monthly injections of testosterone enanthate and in females at age 11 to 12 years with 17 beta-estradiol or estradiol valerate and later by cycling with progesterone. Fertility in both sexes is possible with administration of gonadotropins. ACTH deficiency is treated with hydrocortisone, with dose adjustments as needed for illness and/or surgeries.

Surveillance: IGF1, total T4, free T4, estradiol (in females) or testosterone (in males), and cortisol levels every three to four months; measure PrL at diagnosis.

Agents/circumstances to avoid: Thyroid hormone replacement in those with untreated adrenal insufficiency; for individuals with GH deficiency, the lowest safe dose of hydrocortisone is used to avoid interfering with the growth response to growth hormone therapy.

Evaluation of relatives at risk: In younger sibs, perform molecular genetic testing to enable early diagnosis and treatment; otherwise monitor growth for evidence of growth failure.

Genetic counseling

PROP1-related CPHD is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for a *PROP1* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of inheriting neither of the familial *PROP1* pathogenic variants. Once the *PROP1* pathogenic variants have been identified in an affected family member, carrier testing for at-risk relatives, prenatal testing for a pregnancy at increased risk, and preimplantation genetic testing are possible.

Diagnosis

Suggestive Findings

PROP1-related combined pituitary hormone deficiency (CPHD) **should be suspected** in individuals with the following clinical, laboratory, imaging, and family history features.

CPHD is defined as growth hormone (GH) deficiency AND deficiency of at least one of the following other pituitary hormones:

- Thyroid-stimulating hormone (TSH)
- The two gonadotropins, luteinizing hormone (LH) and follicle-stimulating hormone (FSH)
- Prolactin (PrL)
- Adrenocorticotropic hormone (ACTH) (Deficiency develops in ~50% of individuals.)

Clinical features

- **GH deficiency.** Proportionate moderate-to-severe short stature with growth deceleration

- **TSH deficiency.** Although TSH deficiency can present shortly after birth, it usually occurs with or following the onset of GH deficiency. Hypothyroidism is usually mild, without clinical features of congenital hypothyroidism, but likely contributes to impaired growth velocity.
- **LH and FSH deficiency.** Newborn males with micropenis (stretched penile length <2.5 cm in a term infant), with or without cryptorchidism; adolescent males with onset of puberty after age 14 years or impaired secondary sexual development; adolescent females with lack of breast development or menses by age 13 years
- **PrL deficiency.** Adult females with impaired lactation
- **ACTH deficiency.** Features of chronic ACTH deficiency in children and adults include persistent weakness, abdominal pain, anorexia, and weight loss. Note: Features of acute ACTH deficiency including acute hypotension, dehydration, and shock are not reported.

Laboratory features

- **GH deficiency.** Low basal IGF1 levels; serum GH <7 ng/dL on two provocative tests. Stimuli used for provocative testing for GH deficiency include arginine, clonidine, insulin, insulin-arginine, and glucagon.
- **TSH deficiency** can be present in individuals with apparently normal TSH-T4 axis. Basal serum free T4 is low or repeatedly low-normal and T4 concentration 1.0 µg/dL below normal for age with a low-normal serum TSH (normal: 0.1 mIU/L to 4.5-5.5 mIU/L). Most individuals are diagnosed based on insufficient responses in thyrotropin-releasing hormone (TRH) stimulation tests.
- **LH and FSH deficiency.** Low serum LH and FSH and low serum testosterone in males; low serum estradiol (and/or the lack of progestin-induced withdrawal bleeding) in females age 13 years or older. LH and FSH deficiency are confirmed by subnormal increase in serum LH and FSH following infusion of GnRH in an individual age 13-14 years or older.
- **PrL deficiency.** Serum PrL low or normal
- **ACTH deficiency.** Hyponatremia, hyperkalemia, and hypoglycemia in an acutely ill untreated individual; serum ACTH is inappropriately low in the presence of a low serum concentration of cortisol; normal renin-aldosterone axis. ACTH deficiency is confirmed by subnormal increase in serum ACTH in response to hypoglycemia or corticotropin-releasing hormone, suggesting a pituitary etiology of ACTH deficiency.

Imaging features

- Delayed bone maturation on x-ray examination
- On head MRI, normal pituitary stalk and normal position of posterior lobe; anterior lobe may appear hypoplastic, normal, or diffusely enlarged [Correa et al 2019]. The sella turcica may be normal in size, enlarged, or may appear empty; pituitary imaging findings may mimic those seen in pseudotumor, non-functioning adenoma, craniopharyngioma, or Rathke's pouch cyst. The pituitary may initially be enlarged in childhood, wax and wane in size before reducing in size in adolescence or adulthood, and then undergo complete involution.

Family history is consistent with autosomal recessive inheritance (e.g., affected sibs and/or parental consanguinity). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of *PROP1*-related CPHD **is established** in a proband with suggestive findings and biallelic pathogenic (or likely pathogenic) variants in *PROP1* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of biallelic *PROP1* variants of uncertain

significance (or identification of one known *PROP1* pathogenic variant and one *PROP1* variant of uncertain significance) does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing).

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1). Those with a phenotype indistinguishable from other causes of CPHD are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

Single-gene testing. Sequence analysis of *PROP1* is performed first to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If only one or no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.

Note: Targeted analysis can be considered for founder variants in individuals of Hutterite, Indian, and/or Eastern European ancestry or for individuals from the Iberian Peninsula. See Table 7.

A CPHD multigene panel that includes *PROP1* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

When the phenotype is indistinguishable from many other inherited disorders characterized by CPHD, **comprehensive genomic testing**, which does not require the clinician to determine which gene is likely involved, is an option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in *PROP1*-Related Combined Pituitary Hormone Deficiency

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
PROP1	Sequence analysis [3]	>98% [4, 5]
	Deletion/duplication analysis [6]	<2% [5]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. The common recurring *PROP1* pathogenic variant in which three AG repeats are reduced to two AG repeats (c.301_302delAG) accounts for 55% of alleles in familial cases and 12% of alleles in simplex cases (i.e., single occurrence in a family) of CPHD.
5. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
6. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

Clinical Characteristics

Clinical Description

PROP1-related combined pituitary hormone deficiency (CPHD) is associated with deficiencies of: growth hormone (GH); thyroid-stimulating hormone (TSH); the two gonadotropins, luteinizing hormone (LH) and follicle-stimulating hormone (FSH); prolactin (PrL); and adrenocorticotropic hormone (ACTH). The secretion of all these pituitary-derived hormones declines gradually with age; often the order of appearance of hormone deficiency is GH, LH and FSH, TSH, and then ACTH. The degree of hormone deficiency and the age of onset of the deficiency are variable even within the same family. To date, hundreds of individuals have been identified with *PROP1*-related CPHD [Baş et al 2015, Fritez et al 2015, Rohayem et al 2016, Madeira et al 2017, Gorar et al 2018, Bajuk Studen et al 2019, Correa et al 2019, Bulut et al 2020]. The following description of the phenotypic features associated with this condition is based on reports that included affected adults to account for the later onset of gonadotropin and ACTH deficiency.

Table 2. *PROP1*-Related Combined Pituitary Hormone Deficiency: Frequency of Select Features

Feature	% of Persons w/Feature	Typical Onset	Comment
GH deficiency	100%	9 mos to 8 yrs	
TSH deficiency	50%-100%	Late infancy to childhood	
FSH / LH deficiency	100%	At puberty	Typically identified at puberty
PrL deficiency	30%-80%	3 mos to 14 yrs	
ACTH deficiency	30%-80%	Adolescence to adulthood	

ACTH = adrenocorticotropic hormone; FSH = follicle-stimulating hormone; GH = growth hormone; LH = luteinizing hormone; PrL = prolactin; TSH = thyroid-stimulating hormone

GH deficiency. In general, short stature is the first symptom reported in individuals with *PROP1*-related CPHD. Most affected children have normal birth weight and birth length and an uncomplicated perinatal period. Hypoglycemia in newborns with *PROP1*-related CPHD may rarely occur. Growth deficiency with moderate-to-severe growth deceleration usually develops within the first year of life (height -1.5±0.9 SDs at age 1.5 years) and becomes more prominent later in infancy and early childhood, mainly between ages 1.5 and 3 years (-3.6±1.3 SDs at age 3 years), when parents seek medical assistance. At diagnosis, bone age is usually severely delayed (-4.0 SDs at age 2.5 years) and hands and feet are proportionately small.

Clinical response to exogenous GH usually depends on the severity of GH deficiency, deficiencies of other pituitary hormones, age of onset of growth failure, the time interval between the onset of growth failure and the onset of GH therapy, duration of replacement therapy, and the sex of the affected individual.

If treatment is started early in life, GH therapy is very effective for linear growth to achieve familial expected height. GH therapy has also improved body composition and quality of life in older individuals [Doknic et al 2020].

TSH deficiency. Rarely, hypothyroidism is the presenting finding. Hypothyroidism is usually mild and occurs in later infancy and childhood. Since it is usually not congenital or severe, it is not associated with intellectual disability or other physical findings of congenital hypothyroidism. TSH deficiency can be present in individuals with apparently normal TSH-T4 axis.

FSH and LH deficiency. Newborn males with early-onset gonadotropin deficiency can present with micropenis (stretched penile length <2.5 cm in a term infant) with or without cryptorchidism.

Affected individuals with later onset can have absent or delayed and incomplete secondary sexual development and infertility. Adolescent males may present with small penis, small testes, onset of puberty after age 14 years, and/or cessation of secondary sexual development. Adolescent females may present with lack of breast development or delayed menarche. Some females experience menarche before requiring hormone replacement therapy [Flück et al 1998]. Gonadotropic function can also progressively decline and present as primary or secondary lack of reproductive function. There are reports of spontaneous puberty with decline of gonadotropic function in individuals with p.Arg120Cys, p.Phe88Ser, and c.150delA *PROP1* variants. Impaired gonadotropic function occurs in all individuals with the most common *PROP1* variant, c.301_302delAG.

Gonadotropin deficiency can be the presenting feature, with GH deficiency and TSH deficiency developing later in adulthood [Reynaud et al 2005].

Prolactin (PrL) deficiency generally causes few symptoms, aside from impaired lactation in adult women [Voutetakis et al 2004].

ACTH deficiency most often occurs in adolescence or adulthood. The range of onset of ACTH deficiency is age 11 years to 63 years. Individuals may present with persistent weakness, abdominal pain, anorexia, and weight loss. Neonatal presentation and signs of acute ACTH deficiency have not been described. It appears unlikely that deficiency of the PROP1 transcription factor causes ACTH deficiency directly, but PROP1 may have some role in differentiation or viability of corticotrophs [Araujo et al 2013]. Surveillance is extremely important in all individuals with *PROP1*-related CPHD because adrenal function gradually declines over time, even after more than four decades. Furthermore, as GH replacement can increase cortisol metabolism, it is necessary to be aware of the signs of an unveiled adrenal insufficiency.

Intelligence is usually normal.

Other findings

- Facies are characterized as "immature," with a depressed nasal bridge and relative decrease in the vertical dimensions of the face [Pirinen et al 1994].
- Obesity, rare in childhood, is more common in adulthood.

Genotype-Phenotype Correlations

Limited genotype-phenotype correlations have been identified. Phenotypic variability was observed among individuals with the same pathogenic variants, particularly the presence and age of onset of hypocortisolism, the levels of prolactin, and the results of pituitary imaging [Lemos et al 2006].

- There are reports of spontaneous puberty with decline of gonadotropic function in individuals with *PROP1* variants p.Arg120Cys, p.Phe88Ser, and c.150delA [Flück et al 1998].
- Impaired gonadotropic function occurs in all individuals with the most common *PROP1* variant, c.301_302delAG [Madeira et al 2017].

Prevalence

The prevalence of *PROP1*-related CHPD is estimated at fewer than 1:30,000 individuals, and *PROP1* pathogenic variants are the most common cause of CPHD worldwide. *PROP1* pathogenic variants were found in 6.7% of simplex cases and 48.5% of individuals with familial CPHD [De Rienzo et al 2015]. Incidence of *PROP1* variants in individuals with CHPD varies widely by ethnicity: 70.1% in Lithuania (47/67 individuals with CPHD were found to have biallelic *PROP1* pathogenic variants); approximately 53% in the Brazilian population (16/30 individuals tested), 50.8% in Poland (32/63); 0% in the Netherlands (0/50), the United Kingdom (0/27), Japan (0/71), Korea (0/12), and Australia (0/33).

PROP1-related CHPD may be more common in populations with reported founder variants (see Table 7).

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *PROP1*.

Differential Diagnosis

Table 3 reviews genetic disorders of interest in the differential diagnosis of *PROP1*-related combined pituitary hormone deficiency (CPHD), including:

- Selected genes associated with CPHD;*
- Isolated growth hormone deficiency (which may evolve into CPHD);
- Isolated hypogonadotropic hypogonadism (which may overlap molecularly with CPHD and/or evolve in CPHD).

* More than 30 genes are known to be associated CPHD. Based on 21 studies, pathogenic variants in five genes – *HESX1*, *LHX3*, *LHX4*, *PROP1*, and *POU1F1* – account for 12.4% of CPHD worldwide including 11.2% of simplex cases and 63% of individuals with familial CPHD. Of these five genes, *PROP1* was the most frequently involved, accounting for 6.7% of simplex cases and 48.5% of individuals with familial CPHD [De Rienzo et al 2015].

Note: Some CPHD conditions may present with extrapituitary abnormalities that have not been systematically reported in *PROP1*-related CPHD.

Table 3. Genetic Disorders of Interest in the Differential Diagnosis of *PROP1*-Related Combined Pituitary Hormone Deficiency

Gene	Disorder	MOI	Clinical Characteristics
Combined pituitary hormone deficiency			
GLI2	*GLI2*-related CPHD (OMIM 165230)	AD	CPHD or IGHD; ectopic posterior lobe, polydactyly, midline defects from hypotelorism to holoprosencephaly, cleft lip/palate
HESX1	*HESX1*-related CPHD (OMIM 182230)	AD AR	CPHD or isolated GH deficiency; midline defects, optic nerve hypoplasia, ectopic or normal posterior pituitary lobe & anterior lobe hypoplasia

Table 3. continued from previous page.

Gene	Disorder	MOI	Clinical Characteristics
LHX3	*LHX3*-related CPHD (OMIM 221750)	AR	Cervical spine rigidity, vertebral abnormalities, sensorineural hearing loss. Pituitary is usually hypoplastic but may be normal & occasionally enlarged.
LHX4	*LHX4*-related CPHD (OMIM 262700)	AD	Cerebellar defects (Chiari syndrome), small anterior pituitary, & ectopic posterior lobe (Biallelic pathogenic variants are assoc w/lethal phenotype w/hypopituitarism & respiratory distress.)
POU1F1	*POU1F1*-related isolated or combined CPHD (OMIM 613038)	AR AD	Deficiency of GH, PRL, & variable TSH, rarely IGHD. Hypothyroidism can be congenital & severe, or mild & later in onset; pituitary usually hypoplastic on imaging studies.
Isolated growth hormone deficiency			
GH1	*IGHD1A* (OMIM 262400)	AR	Severe growth failure; affected persons treated w/ exogenous GH often develop anti-GH antibodies.
	IGHD1B (OMIM 612781)	AR	Growth failure is less severe than in IGHD1A & persons usually respond well to exogenous GH.
	IGHD2 (OMIM 173100)	AD	Clinical severity varies. Affected persons usually respond well to exogenous GH, may develop CPHD.
Isolated hypogonadotropic hypogonadism			
Genes	**Disorder**	**MOI**	**Clinical characteristics**
ANOS1, *AXL*, *CCDC14*, *CHD7*, *DUSP6*, *FEZF1*, *FGF8*, *FGF17*, *FGFR1*, *FLRT3*, *GNRH1*, *GNRHR*, *HS6ST1*, *IGSF10* [1], *IL17RD*, *KISS1*, *KISS1R*, *NSMF*, *POLR3B*, *PROK2*, *PROKR2*, *SEMA3A*, *SEMA3E*, *SOX10*, *SPRY4*, *SRA1*, *TAC3*, *TACR3*, *WDR11*	Isolated GnRH hormone deficiency [2]	XL AD AR	Some genes generally assoc w/isolated hypogonadotropic hypogonadism can cause CPHD.

AD = autosomal dominant; AR = autosomal recessive; CPHD = combined pituitary hormone deficiency; GH = growth hormone; GnRH = gonadotropin-releasing hormone; IGHD = isolated growth hormone deficiency; MOI = mode of inheritance; PrL = prolactin; TSH = thyroid-stimulating hormone; XL = X-linked

1. Howard et al [2016]

2. Pathogenic variants in more than 30 genes account for about half of all isolated GnRH deficiency; the genetic cause is unknown in about 50% of persons with isolated GnRH deficiency.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in each individual with newly diagnosed *PROP1*-related combined pituitary hormone deficiency (CPHD), the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with *PROP1*-Related Combined Pituitary Hormone Deficiency

System/Concern	Evaluation	Comment
Endocrine	Growth & growth velocity assessment	
	• Basal IGF1 • Basal & stimulated GH	
	Basal total T4, free T4, & TSH	
	• Clinical assessment for micropenis in newborn males • Clinical assessment of pubertal development & secondary sexual characteristics in newly diagnosed adolescents/adults • Assessment of amenorrhea or irregular menses in women • Assessment of infertility • LH & FSH measured at beginning of pubertal age	
	Basal prolactin	
	AM cortisol & after synthetic ACTH, ITT (glucagon test)	
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of *PROP1*-related CPHD to facilitate medical & personal decision making

ITT = insulin tolerance test; MOI = mode of inheritance
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

The main principle of treatment in *PROP1*-related CPHD is replacement hormone therapy under the guidance of endocrinology.

Table 5. Treatment of Manifestations in Individuals with *PROP1*-Related Combined Pituitary Hormone Deficiency

Manifestation/ Concern	Treatment	Considerations/Other
Growth hormone deficiency	Subcutaneous injection of biosynthetic (i.e., recombinant) GH (rhGH) started as soon as GH deficiency is identified. • The initial dose of rhGH is based on body weight in childhood. • The dose ↑s w/↑ body weight to a maximum during puberty. • When final height is achieved, rhGH dose is ↓ to 0.2-0.4 mg/d for persons age <60 yrs & 0.1-0.2 mg/d for person age >60 yrs.	• The ideal rhGH dose will raise & maintain IGF1 levels to between mean & upper limit of normal. [1] • There is ↑ support for rhGH treatment in young adults because of possible effects on fat metabolism, lean body mass, & bone mineral density. [2]
TSH deficiency	Thyroid hormone replacement (L-thyroxine) 1-3 µg/kg/day	Thyroid hormone replacement should not be initiated until adrenal function has been assessed & adrenal insufficiency treated, if present.
Micropenis in male infants	50 mg testosterone enanthate intramuscularly every 4 wks for a total of 3-4 doses	

Table 5. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/Other
LH & FSH deficiency (in those w/**treated** GH deficiency & normal growth before adolescence)	Sex steroid replacement to induce secondary sex characteristics • In males: starting at 12-13 yrs, monthly injections of 100 mg testosterone enanthate, gradually ↑ by 50 mg every 6 mos to a dose of 200-300 mg/mo • In females: starting at 11-12 yrs, 17 beta-estradiol or estradiol valerate, cycling w/progesterone (medroxyprogesterone acetate, 5-10 mg/d) & micronized progesterone (200 mg/d from 1st to 12th day of each month)	Treatment w/sex steroids is often continued to maintain secondary sex characteristics.
LH & FSH deficiency (in those w/**untreated** GH deficiency)	Sex hormone replacement is given in lower doses & started at a later age to ensure maximal growth before epiphyseal closure.	
Infertility	Gonadotropin replacement	Note: Infertility in persons w/*PROP1*-related CPHD is secondary to hypogonadotropic hypogonadism; thus, appropriate treatment is gonadotropin replacement rather than use of clomiphene citrate, which requires an intact pituitary gland.
ACTH deficiency	• Long-term mgmt: 8-10 mg/m^2 oral hydrocortisone per 24 hrs divided into 2 or 3 doses. • For minor stress (e.g., fever, minor illness), hydrocortisone dose is doubled or tripled until illness has resolved. • For major stress (e.g., surgery, significant illness), hydrocortisone is ↑ to 50-100 mg & administered parenterally w/fluid replacement.	For persons w/GH deficiency, the lowest safe dose of hydrocortisone is used to avoid interfering w/growth response to GH therapy.

1. Growth Hormone Research Society [2000] (full text)
2. Ho et al [2007] (full text), Fleseriu et al [2016]

Surveillance

Table 6. Recommended Surveillance for Individuals with *PROP1*-Related Combined Pituitary Hormone Deficiency

System/Concern	Evaluation	Frequency
Growth	IGF1	Every 3-4 mos
TSH deficiency	Total T4, free T4	
LH/FSH deficiency	Estradiol (in females) or testosterone (in males)	
PrL deficiency	Prolactin	At diagnosis
ACTH deficiency	Cortisol levels	Every 3-4 mos

ACTH = adrenocorticotropic hormone; FSH = follicle-stimulating hormone; GH = growth hormone; LH = luteinizing hormone; PrL = prolactin; TSH = thyroid-stimulating hormone

Agents/Circumstances to Avoid

Thyroid hormone replacement should not be initiated until adrenal function has been assessed and adrenal insufficiency is treated if present.

For individuals with GH deficiency, the lowest safe dose of hydrocortisone is used to avoid interfering with the growth response to growth hormone therapy.

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of younger sibs of an affected individual in order to identify as early as possible those who would benefit from prompt initiation of hormone replacement therapy and surveillance.

For younger sibs who have not undergone molecular genetic testing, monitoring growth for evidence of growth failure is appropriate. Of note, affected sibs usually have extreme short stature because of thyroid hormone deficiency and GH deficiency.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Long-acting GH preparations are being developed to improve adherence by decreasing the frequency of GH injections from daily to weekly, biweekly, or monthly. However, several questions need to be addressed including the methods of dose adjustment, the timing of IGF1 monitoring, safety, efficacy, and cost effectiveness [Miller et al 2020].

Newer glucocorticoid replacement alternatives are under development. Medications with a modified release (Chonocort®) and dual release (Plenadren®) of hydrocortisone have been studied. Their pharmacokinetics promote corticoid bioavailability closer to circadian production [Paragliola & Corsello 2018, Garmes et al 2021].

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

PROP1-related combined pituitary hormone deficiency (CPHD) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are presumed to be heterozygous for a *PROP1* pathogenic variant.
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for a *PROP1* pathogenic variant and to allow reliable recurrence risk assessment.
- If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, it is possible that one of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017]. If the proband appears to have homozygous pathogenic variants (i.e., the same two pathogenic variants), additional possibilities to consider include:

- A single- or multiexon deletion in the proband that was not detected by sequence analysis and that resulted in the artifactual appearance of homozygosity;
- Uniparental isodisomy for the parental chromosome with the pathogenic variant that resulted in homozygosity for the pathogenic variant in the proband.

- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for a *PROP1* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of inheriting neither of the familial *PROP1* pathogenic variants.
- Intrafamilial clinical variability may be observed between sibs with the same pathogenic variants [Lemos et al 2006, Madeira et al 2017].
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband

- Fertility in both females and males with *PROP1*-related CPHD is possible with administration of gonadotropins. Two females with *PROP1* pathogenic variants had ovulation induction and successful pregnancy outcome without GH replacement. They were not able to lactate [Voutetakis et al 2004].
- The offspring of an individual with *PROP1*-related CPHD are obligate heterozygotes (carriers) for a pathogenic variant in *PROP1*.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a *PROP1* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *PROP1* pathogenic variants in the family.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.

Prenatal Testing and Preimplantation Genetic Testing

Once the *PROP1* pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Child Growth Foundation**
  United Kingdom
  Phone: 0208 995 0257
  Email: nfo@childgrowthfoundation.org
  www.childgrowthfoundation.org
- **Human Growth Foundation**
  www.hgfound.org
- **MAGIC Foundation**
  Phone: 800-362-4423
  Email: contactus@magicfoundation.org
  www.magicfoundation.org
- **MedlinePlus**
  Combined pituitary hormone deficiency
- **The Pituitary Foundation**
  United Kingdom
  Phone: 0117 370 1320
  Email: enquiries@pituitary.org.uk
  www.pituitary.org.uk

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. PROP1-Related Combined Pituitary Hormone Deficiency: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
PROP1	5q35.3	Homeobox protein prophet of Pit-1	PROP1 database	PROP1	PROP1

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for PROP1-Related Combined Pituitary Hormone Deficiency (View All in OMIM)

262600	PITUITARY HORMONE DEFICIENCY, COMBINED, 2; CPHD2
601538	PROP PAIRED-LIKE HOMEOBOX 1; PROP1

Molecular Pathogenesis

PROP1 encodes the homeobox protein prophet of PIT-1, which has DNA binding and transcriptional activation ability. Expression of homeobox protein prophet of PIT-1 is required for the ontogenesis of pituitary gonadotropes, somatotropes, lactotropes, and thyrotropes needed for the normal production of growth hormone (GH), thyroid-stimulating hormone (TSH), luteinizing hormone (LH), follicle-stimulating hormone (FSH), and

prolactin (PrL). Two conserved basic regions within the homeodomain are important for localization to the nucleus, DNA binding, and target gene activation. Missense variants in these two regions of *PROP1* result in CPHD, indicating the importance of these conserved sequences [Guy et al 2004].

Mechanism of disease causation. Loss of function with reduced or absent DNA binding and transcriptional activation ability

Table 7. Notable *PROP1* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change (Alias [1])	Predicted Protein Change	Comment [Reference]
NM_006261.5 NP_006252.4	c.112_124del	p.Ser38ProfsTer123	Possible founder variant on Indian subcontinent [Turton et al 2005]
	c.301_302delAG (c.296_297delGA)	p.Leu102CysfsTer8	Common variant in Europe & Latin America [Dusatkova et al 2016]; founder variant in Lithuania [Navardauskaite et al 2014] & Hutterite population [Wu et al 1998]; see also Genotype-Phenotype Correlations.
	c.150delA	p.Arg53AspfsTer112	Common variant in several populations [Krzisnik et al 1999, Dusatkova et al 2016]; see also Genotype-Phenotype Correlations.
	c.263T>C	p.Phe88Ser	Osorio et al [2000]; see Genotype-Phenotype Correlations.
	c.358C>T	p.Arg120Cys	Wu et al [1998]; see Genotype-Phenotype Correlations.

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. Variant designation that does not conform to current naming conventions

Chapter Notes

Author Notes

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