GENEReviews

Funded by the NIH · Developed at GeneTests (www.genetests.org), University of Washington, Seattle

PROP1- Related Combined Pituitary Hormone Deficiency (CPHD)

[*CPHD*]

John A Phillips III, MD
Division of Medical Genetics
Vanderbilt University Medical Center
Nashville
john.phillips@vanderbilt.edu

Cindy Vnencak-Jones, PhD
Molecular Diagnostic Laboratory
Vanderbilt University Medical Center
Nashville
cindy.vnencak-jones@vanderbilt.edu

Lawrence C Layman, MD
Reproductive Endocrinology and Infertility Genetics
Medical College of Georgia
Augusta
llayman@mail.mcg.edu

Initial Posting: December 7, 2000.
Last Update: November 21, 2005.

Summary

Disease 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 adrenocorticotrophic hormone (ACTH). Most affected individuals are ascertained because of growth failure and failure to thrive starting in infancy or early childhood (range: ~9 months to ~8 years). Hypothyroidism is usually mild and occurs in later infancy and childhood. Affected individuals can have absent or delayed and incomplete secondary sexual development with infertility. 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.

Diagnosis/testing. Testing for deficient secretion of GH, TSH, LH, FSH, PrL, and ACTH establishes the diagnosis of CPHD; *PROP1* is the only gene associated with *PROP1*-related CPHD. Targeted mutation analysis for the common recurring deletion in which three AG repeats are reduced to two repeats is available clinically. This mutation accounts for 55% of familial cases of CPHD and 12% of nonfamilial cases of CPHD.

Management. GH deficiency is treated with injection of biosynthetic growth hormone from the time of diagnosis until approximately 17 years of age or longer. TSH deficiency is treated by thyroid hormone replacement in the form of L-thyroxine. Infants with micropenis are treated with testosterone. Hormone replacement to induce secondary sex characteristics can be initiated in males at 12 to 13 years with monthly injections of testosterone enanthate and in females at 11 to 12 years with conjugated estrogens or ethinyl estradiol and later by cycling with estrogen and progesterone. Children with untreated growth hormone deficiency receive sex hormone replacement in lower doses at a later age. Fertility in both sexes is possible with

administration of gonadotropins. Management of ACTH deficiency is treated with oral hydrocortisone.

Genetic counseling. *PROP1*-related CPHD is inherited in an autosomal recessive manner. At conception, the sibs of an affected individual have a 25% chance of being affected, a 50% chance of being asymptomatic carriers, and a 25% chance of being unaffected and not carriers. Once an at-risk sib is known to be unaffected, the chance of his/her being a carrier is 2/3. Prenatal testing for pregnancies at 25% risk for *PROP1*-related CPHD is possible when both disease-causing *PROP1* mutations are known.

Diagnosis

Clinical Diagnosis

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 adrenocorticotrophic hormone (ACTH).

Affected individuals are usually ascertained because of short stature; diagnosis requires the presence of GH deficiency and at least one other pituitary hormone deficiency (Wu 1998) **and/or** identification of two *PROP1* mutations.

Growth hormone (GH) deficiency is suspected in children with the following features:

- Neonatal hypoglycemia

  and/or

- Proportionate short stature and delayed bone maturation (in the absence of an inherited bone dysplasia or chronic disease) with the following growth patterns [Rosenfeld 1996]:
  - Severe short stature with height more than three standard deviations (SD) below the mean for age

    or

  - Moderate short stature with height two to three SD below the mean for age and growth deceleration with height velocity less than 25th percentile for age

    or

  - Severe growth deceleration with height velocity less than 5th percentile for age

Thyroid-stimulating hormone (TSH) deficiency is suspected in children with growth failure, poor weight gain, and delayed bone maturation. Infants with congenital hypothyroidism rarely have signs in the first month of life. Signs and symptoms that may be apparent later are large posterior fontanelle (more than one centimeter in diameter), jaundice that lasts for more than one week after birth, macroglossia, hoarse cry, distended abdomen, umbilical hernia, and hypotonia.

Luteinizing hormone (LH) and follicle-stimulating hormone (FSH) deficiency is suspected in the following:

- Newborn males with micropenis (stretched penile length less than 2.5 cm in a term infant) without hypospadias with or without cryptorchidism

- Adolescent males with onset of puberty after age 14 years or cessation of secondary sexual development
- Adolescent females with lack of breast development or menses by age 14 years

Prolactin (PrL) deficiency is suspected in females with impaired lactation.

Adrenocorticotrophic hormone (ACTH) deficiency is suspected in children with persistent weakness, fever, abdominal pain, anorexia, and weight loss. Signs of acute ACTH deficiency include acute hypotension, dehydration, and shock accompanied by hyponatremia, hyperkalemia, and hypoglycemia.

Testing

Testing concomitantly for deficiency secretion of GH, TSH, LH, FSH, PrL, and ACTH should be done for diagnosis and management [Phillips 1995, Rimoin & Phillips 1997].

Deficiencies of all pituitary hormones may be assessed simultaneously using the triple test (exogenous GnRH [gonadotropin-releasing hormone], TRH [thyrotropin-releasing hormone], and insulin-induced hypoglycemia). GnRH should increase FSH and LH. TRH should increase TSH and PrL. Hypoglycemia (with a blood sugar less than 40 mg/dL or half the baseline value) should result in an increase in the stress hormones prolactin, growth hormone, and cortisol.

Growth hormone (GH) deficiency. Even in the appropriate clinical setting, the diagnosis of GH deficiency remains problematic because of the difficulty in measuring physiologic GH secretion. Provocative tests of GH secretion are widely used in the diagnosis of GH deficiency, although they are associated with a high false-positive rate. Stimuli include exercise, arginine, L-Dopa, clonidine, insulin, insulin-arginine, glucagon, and propranolol. A peak serum concentration of GH greater than 7-10 ng/mL on one test rules out the diagnosis of GH deficiency.

- Confirmatory study: serum concentration of GH less than 7-10 ng/dL on two provocative tests

Thyroid-stimulating hormone (TSH) deficiency

- Low serum T_4 concentration 1.0 µg/dL below normal for age with a low serum TSH concentration (normal: 0.1 mU/L to 4.5-5.5 mU/L)
- Confirmatory study: subnormal increase in serum concentration of TSH 30 minutes after infusion of TRH

Note: All newborn screening programs for congenital hypothyroidism screen for elevated TSH; only those programs that also use initial T_4 measurements detect infants with low TSH.

Luteinizing hormone (LH) and follicle-stimulating hormone (FSH) deficiency

- Low serum concentrations of LH, FSH, and low serum testosterone concentration in males or low serum estradiol concentration [and/or the lack of a progestin-induced withdrawal bleeding] in females 14 years of age or older
- Confirmatory study: subnormal increase in serum concentration of LH and FSH following infusion of GnRH in an individual 14 years of age or older

Note: No absolute cutoff values have been established.

Prolactin (PrL) deficiency

- Very low or undetectable baseline prolactin
- Confirmatory study: absent response to TRH stimulation

Adrenocorticotrophic hormone (ACTH) deficiency

- Low serum concentration of sodium and glucose and elevated serum concentration of potassium in an acutely ill individual
- Serum ACTH concentration that is inappropriately low in the face of a low serum concentration of cortisol (Note: The blood for the ACTH assay needs to be collected properly on ice and sent to the laboratory expeditiously.)
- Normal renin-aldosterone axis
- Confirmatory study: subnormal increase in serum ACTH concentration in response to CRH (corticotropin releasing hormone) suggests a pituitary etiology of ACTH deficiency. Insulin-induced hypoglycemia may also be used, but a subnormal response could indicate a hypothalamic or a pituitary cause.

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Molecular Genetic Testing—Gene. *PROP1* is the only gene associated with *PROP1*-related CPHD.

Molecular genetic testing: Clinical uses

- Confirmatory diagnostic testing
- Carrier testing
- Prenatal diagnosis

Molecular genetic testing: Clinical method

Targeted mutation analysis. The common recurring deletion in which three AG repeats are reduced to two repeats (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.

Sequence analysis. The mutation detection rate varies by study suggesting either bias in ascertainment in some studies or variation in the frequency of PROPI mutations between populations of different ethnic origins.

- In several international centers (UK, India, and Poland), *PROP1* mutations were identified in only 1-2% of individuals representing simplex cases of CPHD and almost 30% of familial cases [Turton et al 2005].
- No *PROP1* mutations were identified in ten simplex cases and 12 familial cases of CPHD in the UK [Rainbow et al 2005].
- No *PROP1* mutations were identified in 32 unrelated CPHD probands from Austrailia [McLennan et al 2003] or 27 children with CPHD from 26 families from the West Midlands, UK [Rainbow et al 2005].

Table 1 summarizes molecular genetic testing for this disorder.

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

Test Method	Mutations Detected	Mutation Detection Rate [1]	Test Availability
Targeted mutation analysis	301-302delAG	Familial 55% [2] Simplex 0-12% [3]	Clinical Testing
Sequence analysis	*PROP1* sequence alterations	~0-25%	

1. These rates indicate ranges
2. Familial: More than one affected family member
3. Simplex: Single occurrence in a family

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Genetically Related Disorders

No other phenotypes are associated with mutations in *PROP1*.

Note: There is no evidence that individuals with isolated deficiency of gonadotropins (hypogonadotropic hypogonadism) have mutations in *PROP1* [Park et al 2004], although this might be presumed to be a milder phenotypic variant than full CPHD.

Clinical Description

Natural History

PROP1 gene mutations are associated with deficiencies of growth hormone (GH), thyroid-stimulating hormone (TSH), gonadotropins (FSH and LH), prolactin (PrL), and adrenocorticotrophic 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 ACTH. The degree of hormone deficiency and the age of onset of the deficiency are variable even within the same family. In a follow up study of nine individuals with *PROP1* mutations, all seven who had reached the age of puberty required steroid hormone replacement therapy. Repeated testing of pituitary function indicated a decline over time; all individuals developed some degree of adrenal insufficiency [Bottner et al 2004].

Most affected children have normal birth weight and birth length and an uncomplicated perinatal period. Growth failure and failure to thrive begin in infancy or early childhood (range: ~9 months to ~8 years). Rarely, hypothyroidism is the presenting finding [Fluck et al 1998].

Individuals with *PROP1*-related CPHD who have untreated growth hormone deficiency have proportional short stature (i.e., less than four centimeters difference between length of arm span and height) with proportionately small hands and feet. Height is usually profoundly reduced, with SDS scores of more than -3.7 [Bottner et al 2004; Reynaud, Chadli-Chaieb et al 2004].

Affected individuals can have absent or delayed and incomplete secondary sexual development with infertility.

- Males usually have a small penis and small testes.
- Some females experience menarche before requiring hormone replacement therapy [Fluck et al 1998].

Severe deficiency of GH and insulin-like growth factor 1 (IGF-1) with mild hypothyroidism and absence of secondary sexual development result in significant growth failure. In one

Brazilian family with eight affected individuals, adult heights ranged from -5.9 to -9.6 SD below the mean.

Hypothyroidism is usually mild and occurs in later infancy and childhood. Since it is usually not congenital or severe, it is not associated with mental deficiency.

It was initially thought that ACTH deficiency was uncommon and, when present, usually occurred in adolescence or adulthood. However, longer follow-up has shown that some degree of adrenal failure may occur in most individuals with *PROP1* mutations [Bottner et al 2004].

An 8° to 20° limitation of extension of the elbows that increases with age has been observed. Facies are characterized as "immature," with a depressed nasal bridge and relative decrease in the vertical dimensions of the face.

Obesity is uncommon in childhood and is more common in adulthood.

Hypoglycemia is not usually reported. Intelligence is normal.

On imaging studies, the pituitary may initially appear diffusely enlarged in childhood and then reduced in size in adolescence or adulthood [Mendonca et al 1999; Riepe et al 2001; Reynaud, Chadli-Chaieb et al 2004; Tatsumi et al 2004; Voutetakis, Argyropoulou et al 2004; Voutetakis, Maniati-Christidi et al 2004].

The sella turcica may be normal in size or enlarged, or may appear "empty."

Genotype-Phenotype Correlations

No genotype-phenotype correlations exist.

Penetrance

The clinical phenotype of *PROP1* deficiency is variable, even among individuals with the same mutations. Variation is observed in the onset of pleiotropic features, the age at diagnosis, and the severity of symptoms resulting from deficiencies of PRL, LH, FSH, GH, or TSH [Fluck et al 1998].

Anterior pituitary function including adrenal function can deteriorate over time such that penetrance is age dependent.

Prevalence

The frequency of pituitary dwarfism is estimated to be about 1/4000 in England and the US. The proportion of individuals with pituitary dwarfism that have CPHD ranges from 43% to 63%, suggesting that the frequency of CPHD is about 1/8000.

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

While short stature, delayed growth velocity, and delayed skeletal maturation are all seen with GH deficiency, none of these symptoms or signs is specific for GH deficiency. Therefore, affected individuals should be evaluated for other, systemic diseases associated with short stature before doing provocative tests to document GH deficiency.

Combined Pituitary Hormone Deficiencies (CPHD)

While many individuals with pituitary dwarfism have a craniopharyngioma or other non-genetic cause, 7% to 12% of individuals have an affected first-degree relative, suggesting that many cases are the result of genetic factors [Phillips 1995]. Bottner et al (2004) concluded that 50% of CPHD has a genetic basis and that half of genetic cases are caused by *PROP1* mutations. Familial CPHD can be inherited in an autosomal recessive, autosomal dominant, or X-linked recessive manner. To date, the genes *PROP1*, *POU1F1* (formerly *PIT1*), *HESX1*, *LHX3*, and *LHX4* have been associated with familial CPHD [Dattani et al 1998; Dattani 2003; Kim et al 2003; McLennan et al 2003; Reynaud, Saveanu et al 2004].

***POU1F1* (formerly *PIT1*).** Mutations of the *POU1F1* gene causing CPHD can be inherited in either an autosomal recessive or autosomal dominant manner. *POU1F1* mutations are associated with deficiencies of growth hormone and prolactin and variable deficiency of the ß subunit of TSH. Of note, *POU1F1* is also associated with isolated growth hormone deficiency [Dattani 2003].

Most affected individuals have normal birth weight and birth length and an uncomplicated perinatal course. Growth hormone deficiency is usually severe and most individuals have growth failure in early infancy.

Affected individuals have proportional short stature and distinctive facies characterized by prominent forehead, marked midface hypoplasia with depressed nasal bridge, deep-set eyes, and short nose with anteverted nostrils [Aarskog et al 1997]. Hypothyroidism can be congenital or can be mild and later onset; progressive loss of TSH occurs over time.

The pituitary usually appears hypoplastic on imaging studies.

***HESX1*.** *HESX1* is expressed in the thickened layer of oral ectoderm that gives rise to the Rathke pouch, the primordium of the anterior pituitary. Down-regulation of *HESX1* coincides with the differentiation of pituitary-specific cell types. Dattani et al (1998) found a missense *HESX1* mutation (R53C) in the homozygous state in a brother and sister with septo-optic dysplasia, agenesis of the corpus callosum, and CPHD (OMIM 182230). More recently, other *HESX1* mutations have been identified, with both autosomal dominant and autosomal recessive inheritance [Cohen et al 2003].

Optic nerve hypoplasia and CPHD. Benner et al (1990) reported one of the few familial occurrences of septo-optic dysplasia: a brother and sister with bilateral optic nerve hypoplasia, absent septum pellucidum, and partial pituitary insufficiency.

Ataxia and CPHD. Ataxia occurs in several forms of familial hypopituitarism.

- Neuhauser & Opitz (1975) reported ataxia and hypogonadism in two brothers and two sisters of a 15-member consanguineous family. The onset of cerebellar ataxia was from 12-20 years in three sibs and 33-38 years in one. Hypogonadotropic hypogonadism caused failure of maturation of secondary sexual characteristics and infertility.
- Bhatia et al (1993) reported an individual with spinocerebellar ataxia, hypogonadism, and short stature with GH, LHRH, and PrL deficiencies.
- Limber et al (1989) described two families with autosomal recessive spinocerebellar ataxia, hypogonadotropic hypogonadism, and choroidal dystrophy.
- Erdem et al (1994) reported a boy, whose parents were first cousins, with cerebellar ataxia, hypogonadotropic hypogonadism, and chorioretinopathy.

Abnormal sella turcica and CPHD. Ferrier & Stone (1969) described two sisters with severe growth retardation from infancy, hypoglycemia, deficiencies of GH, TSH, and ACTH, short stature, and very small sella turcica. Parks et al (1978) described autosomal recessive hypopituitarism with large sella turcica. Serum concentration of GH was low and basal serum concentration of TSH was low despite hypothyroidism.

Chromosomal abnormalities and CPHD. A variety of chromosomal anomalies have been reported in individuals with hypopituitarism including del 18p11 [Boudailliez et al 1983], 8p-, the balanced translocation X;18 (q22.3; q23) [Larizza et al 1993], and paracentric inversion of the short arm of chromosome 1 [Siegel et al 1995].

Isolated Growth Hormone Deficiency

CPHD needs to be differentiated from isolated growth hormone deficiency (IGHD).

IGHD IA and IB are caused by mutations in the *GH1* gene and are inherited in an autosomal recessive manner. In IGHD 1A, deletions, frameshifts, and nonsense mutations lead to GH deficiency with severe growth failure; affected individuals often develop anti-GH antibodies when given exogenous GH. In IGHD IB, splice site mutations are responsible for low, but detectable, levels of GH. Growth failure is less severe than in IGHD IA, and individuals usually respond well to exogenous GH.

IGHD II is caused by mutations in *GH1* and inherited in an autosomal dominant manner. Splice site or missense mutations have a dominant-negative effect. The clinical severity of IGHD II is variable between kindreds. Affected individuals usually respond well to exogenous GH.

Management

Evaluations at Initial Diagnosis to Establish the Extent of Disease

Because treatment of one hormone deficiency can precipitate symptoms of another hormone deficiency, it is important to evaluate each individual newly diagnosed with CPHD for deficiencies of GH, TSH, PRL, LH, FSH, and ACTH.

- Evaluation of LH and FSH production is more relevant in postpubertal individuals, particularly if sexual development is incomplete or if women display hypoestrogenic amenorrhea.
- A total T_4 assay can be used to evaluate thyroid hormone production.
- A.M. cortisol can be used to evaluate adrenal hormone production.

Treatment of Manifestations

Individuals with known deficiencies

- **Growth hormone.** GH deficiency is treated by subcutaneous injection of biosynthetic (i.e., recombinant) GH. To obtain an optimal outcome, replacement therapy should be started as soon as the diagnosis of GH deficiency is established. The initial dose of recombinant GH is based on body weight, but the exact dose and the frequency of administration vary by protocol. The dose increases with increasing body weight to a maximum during puberty and is usually discontinued by approximately 17 years of age [Ranke 1995, Rosen et al 1995]. Some evidence suggests that taking GH for longer periods of time or even for life may be beneficial.

  Clinical response to exogenous GH usually depends upon the etiology and severity

of the GH deficiency, 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 [Blethen et al 1997].

- **LH and FSH**
  - Infants with micropenis are treated with 50 mg testosterone enanthate intramuscularly every four weeks for a total of three to four doses.
  - If GH deficiency is present and if the child's growth normalizes before adolescence, it is appropriate to begin sex steroid replacement to induce secondary sex characteristics.
  - In males, this can be initiated at 12 to 13 years with monthly injections of 100 mg testosterone enanthate, gradually increasing by 50 mg every six months to a dose of 200 to 300 mg per month.
  - In females, this can be initiated at 11 to 12 years with conjugated estrogens or ethinyl estradiol, eventually cycling with estrogen and progesterone.
    - If the child has untreated growth hormone deficiency, the sex hormone replacement is given in lower doses and started at a later age to ensure maximal growth before epiphyseal closure.
    - Usually sex steroids are used to maintain secondary sex characteristics.
    - Fertility in both females and males is possible with administration of gonadotropins [Voutetakis, Sertedaki et al 2004].
- **TSH.** TSH deficiency is treated by thyroid hormone replacement in the form of L-thyroxine at a dose of approximately 1-3 µg/kg/day given orally once a day. Of note, thyroid hormone replacement should not be initiated until adrenal function has been assessed and adrenal insufficiency is treated if present.
- **ACTH.** Long-term management is usually 10-15 mg/M^2 oral hydrocortisone per 24 hours divided into three doses.
  - For individuals with GH deficiency, the lowest safe dose of hydrocortisone is used to avoid interfering with the growth response to growth hormone therapy.
  - For minor stress such as fever or minor illness, the dose of hydrocortisone is doubled or tripled until the illness has resolved.
  - For major stress, such as surgery or significant illness, hydrocortisone is increased to 40 to 100 mg/M^2 and administered parenterally.

Surveillance

- For individuals treated with GH, regular follow-up for potential complications, including aggravation of pre-existing diabetes mellitus, arthralgia, edema, slipped femoral epiphysis, premature ephyseal closure, and pseudotumor cerebri
- Regular follow-up to document normal thyroid function while on thyroid hormone replacement therapy
- Although no protocols for the timing of screening have yet been established, surveillance is appropriate for the following:

- LH and FSH production in postpubertal individuals, particularly if sexual development is incomplete or if women display hypoestrogenic amenorrhea
- The development of adrenal failure. Although specific guidelines have not been established, it is probably reasonable to follow affected individuals at least yearly or to evaluate them promptly if symptoms of deficiency occur. Of note, in the study of Bottner et al (2004) that documented decrease of peak serum cortisol concentration over time most individuals tested two to four times over 3-20 years.

Testing of Relatives at Risk

If both *PROP1* mutations are identified in a proband, it is appropriate to perform molecular genetic testing on younger sibs to identify those at risk for multiple pituitary hormone deficiencies to enable early treatment.

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 and growth hormone deficiency.

Therapies Under Investigation

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

Other

Because infertility in individuals with *PROP1*-related CPHD is secondary to hypogonadotropic hypogonadism, appropriate treatment consists of gonadotropin replacement rather than the use of clomiphene citrate, which requires an intact pituitary gland.

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

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

Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes and, therefore, carry a single copy of a disease-causing mutation in the *PROP1* gene.
- Heterozygotes are asymptomatic.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and having two normal *PROP1* alleles.
- Once an at-risk sib is known to be unaffected, the chance of his/her being a carrier is 2/3.
- Heterozygotes (carriers) are asymptomatic.

Offspring of a proband

- Fertility is reduced in individuals with *PROP1*-related CPHD.
- If an individual with *PROP1*-related CPHD were fertile, each offspring would be an obligate heterozygote (carrier) for a disease-causing mutation in the *PROP1* gene.
- Heterozygotes are asymptomatic.

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

Carrier Detection

Carrier testing is available on a clinical basis once the disease-causing *PROP1* mutations are identified in the proband.

Related Genetic Counseling Issues

Family planning. The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal testing is before pregnancy.

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which the sensitivity of currently available testing is less than 100%. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

Prenatal diagnosis for pregnancies at increased risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15-18 weeks' gestation or chorionic villus sampling (CVS) at about 10-12 weeks' gestation. Both disease-causing alleles of an affected family member must be identified before prenatal testing can be performed.

Requests for prenatal testing for conditions such as *PROP1*-related combined pituitary hormone deficiency that do not affect intellect and are associated with a good prognosis with early treatment are not common. Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. Although most centers would consider decisions about prenatal testing to be the choice of the parents, careful discussion of these issues is appropriate.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutations have been identified in an affected family member in a research or clinical laboratory. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of PROP1-Related Combined Pituitary Hormone Deficiency

Gene Symbol	Chromosomal Locus	Protein Name
PROP1	5q	Homeobox protein prophet of PIT-1

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for PROP1-Related Combined Pituitary Hormone Deficiency

601538	PROPHET OF PIT1, PAIRED-LIKE HOMEODOMAIN TRANSCRIPTION FACTOR; PROP1

Table C. Genomic Databases for PROP1-Related Combined Pituitary Hormone Deficiency

Gene Symbol	Entrez Gene	HGMD
PROP1	5626 (MIM No. 601538)	PROP1

For a description of the genomic databases listed, click here.

Normal allelic variants: The *PROP1* gene contains three exons of 418, 233, and 339 bp and spans 3.54 kb. Transcripts are 990 nucleotides long. Fourteen SNPs of undetermined frequency are in the current NCBI SNP database, including three synonymous, three nonsynonymous, and eight in introns.

Pathologic allelic variants:

- Wu et al (1998) reported five families in which CPHD was caused by homozygosity or compound heterozygosity for inactivating mutations of *PROP1*; these mutations result in *PROP1* gene products with reduced DNA-binding and transcriptional activation ability. The other *PROP1* mutations reported by Wu et al (1998) were a C-to-T transition in codon 120 that encodes an arginine to cysteine substitution and a codon 117 C-to-G transversion that encodes a phenylalanine to isoleucine substitution. The 301-302delAG-marker haplotypes of a closely linked DNA polymorphism (D5S408) differed in each of the families with CPHD, who were from different countries, suggesting that the 301-302delAG mutation is a recurring mutation that may result from DNA slippage repair defects.
- Paracchini et al (2003) described two sibs with compound heterozygosity for R71C/R71H in the first alpha helix of the *PROP1* homeodomain (no in vitro analysis was performed). Both had GH and TSH deficiency and short stature. One sib who was pubertal age lacked breast development.
- Reynaud, Chadli-Chaieb et al (2004) described a homozygous R73Cys mutation in a large, consanguinous kindred. All 12 individuals studied had complete GH deficiency. Eleven of 12 had TSH deficiency and eight of ten had ACTH deficiency. Only two females had spontaneous puberty. In vitro studies revealed that the mutant protein

had 11.5% of transactivation capacity of wild type *PROP1* and was unable to bind a high-affinity DNA sequence.

- Tatsumi et al (2004) reported the first instance of *PROP1* mutations causing CPHD in Japanese individuals. Two sibs presenting with early-onset growth deficiency and deficiencies of GH, TSH, PRL, and gonadotropins were homozygous for a single base deletion in codon 53 (157delA). The protein, if translated, predicts the absence of the DNA binding domain.
- Voutetakis, Maniati-Christidi et al (2004) reported compound heterozygosity for the GA296 deletion and a new nonsense mutation (Q83X) in a neonate with a jaundice and congenital hypothyroidism.
- Voutetakis, Maniati-Christidi et al (2004) reported 15 individuals (age 2.5-45 years) with a variety of different *PROP1* mutations including GA296del/GA296del (7 individuals); GA296del/A150del (2); A150dele/A150del (5) and GA296del/R73H (1).
- Reynaud et al (2005) reported three brothers with hypogonadotropic hypogonadism as a result of homozygosity for the nonsense mutation W194X causing premature truncation of the protein in the transactivation domain. The brothers reached normal adult height but developed GH and TSH deficiencies after age 30 years. In vitro studies revealed that the transactivation capacity of the protein was 34.4% of wild type and suggested that the C-terminal end of the protein plays a role in protein-DNA binding.
- Turton et al (2005) describe considerable phenotypic variability in siblings with CPHD, suggesting that modifying environmental or genetic factors play a role in phenotypic expression of disease. In addition, they report mutation 112-124del as a possible founder mutation from the Indian subcontinent, having identified the mutation in eight individuals from five different families.

No autosomal dominant *PROP1* mutations have been reported to date. (For more information, see Genomic Databases table above.)

Normal gene product: Homeobox protein prophet of PIT-1 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 GH, FSH, LH, PrL, and TSH. Two conserved basic regions (B1 and B2) within the homeodomain are important for localization to the nucleus, DNA binding, and target gene activation. Missense mutations in these two regions of *PROP1* result in CPHD, indicating the importance of these conserved sequences [Guy et al 2004].

Abnormal gene product: Products of mutant *PROP1* genes have reduced DNA-binding and transcriptional activation ability.

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

Human Growth Foundation
997 Glen Cove Avenue, Suite 5

Glen Head, NY 11545
Phone: 800-451-6434
Fax: 516-671-4055
Email: hgf1@hgfound.org
www.hgfound.org

The MAGIC Foundation
6645 West North Avenue
Oak Park, IL 60302
Phone: 708-383-0808
Fax: 708-383-0899
Email: mary@magicfoundation.org
www.magicfoundation.org

References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

Literature Cited

Aarskog D, Eiken HG, Bjerknes R, Myking OL. Pituitary dwarfism in the R271W Pit-1 gene mutation. Eur J Pediatr. 1997;156:829–34. [PubMed: 9392392]

Benner JD, Preslan MW, Gratz E, Joslyn J, Schwartz M, Kelman S. Septo-optic dysplasia in two siblings. Am J Ophthalmol. 1990;109:632–7. [PubMed: 2346191]

Bhatia E, Shukla R, Gupta RK, Misra UK. Multiple pituitary hormone deficiencies in a patient with spinocerebellar ataxia: magnetic resonance imaging and hormonal studies. J Endocrinol Invest. 1993;16:639–42. [PubMed: 8258653]

Blethen SL, Baptista J, Kuntze J, Foley T, LaFranchi S, Johanson A. Adult height in growth hormone (GH)-deficient children treated with biosynthetic GH. The Genentech Growth Study Group. J Clin Endocrinol Metab. 1997;82:418–20. [PubMed: 9024229]

Bottner A, Keller E, Kratzsch J, Stobbe H, Weigel JF, Keller A, Hirsch W, Kiess W, Blum WF, Pfaffle RW. PROP1 mutations cause progressive deterioration of anterior pituitary function including adrenal insufficiency: a longitudinal analysis. J Clin Endocrinol Metab. 2004;89:5256–65. [PubMed: 15472232]

Boudailliez B, Morichon-Delvallez N, Goldfarb A, Pautard JC, Lenaerts C, Piussan C. Solitary upper incisor, hypopituitarism and monosomy 18p chromosome aberration. J Genet Hum. 1983;31:239–42. [PubMed: 6655463]

Cohen RN, Cohen LE, Botero D, Yu C, Sagar A, Jurkiewicz M, Radovick S. Enhanced repression by HESX1 as a cause of hypopituitarism and septooptic dysplasia. J Clin Endocrinol Metab. 2003;88:4832–9. [PubMed: 14557462]

Dattani MT. DNA testing in patients with GH deficiency at the time of transition. Growth Horm IGF Res 13 Suppl A:S122-9. 2003 [PubMed: 12914740]

Dattani MT, Martinez-Barbera JP, Thomas PQ, Brickman JM, Gupta R, Martensson IL, Toresson H, Fox M, Wales JK, Hindmarsh PC, Krauss S, Beddington RS, Robinson IC. Mutations in the homeobox gene HESX1/Hesx1 associated with septo-optic dysplasia in human and mouse. Nat Genet. 1998;19:125–33. [PubMed: 9620767]

Erdem E, Kiratli H, Erbas T, Varli K, Eldem B, Akalin S, Tan E, Topaloglu H, Gedikoglu G. Cerebellar ataxia associated with hypogonadotropic hypogonadism and chorioretinopathy: a poorly recognized association. Clin Neurol Neurosurg. 1994;96:86–91. [PubMed: 8187389]

Ferrier PE, Stone EF Jr. Familial pituitary dwarfism associated with an abnormal sella turcica. Pediatrics. 1969;43:858–65. [PubMed: 4305958]

Fluck C, Deladoey J, Rutishauser K, Eble A, Marti U, Wu W, Mullis PE. Phenotypic variability in familial combined pituitary hormone deficiency caused by a PROP1 gene mutation resulting in the substitution of Arg—>Cys at codon 120 (R120C). J Clin Endocrinol Metab. 1998;83:3727–34. [PubMed: 9768691]

Guy JC, Hunter CS, Showalter AD, Smith TP, Charoonpatrapong K, Sloop KW, Bidwell JP, Rhodes SJ. Conserved amino acid sequences confer nuclear localization upon the Prophet of Pit-1 pituitary transcription factor protein. Gene. 2004;336:263–73. [PubMed: 15246537]

Kim SS, Kim Y, Shin YL, Kim GH, Kim TU, Yoo HW. Clinical characteristics and molecular analysis of PIT1, PROP1,LHX3, and HESX1 in combined pituitary hormone deficiency patients with abnormal pituitary MR imaging. Horm Res. 2003;60:277–83. [PubMed: 14646405]

Larizza D, Maraschio P, Maghnie M, Sampaolo P. Hypogonadism in a patient with balanced X/18 translocation and pituitary hormone deficiency. Eur J Pediatr. 1993;152:424–7. [PubMed: 8319711]

Limber ER, Bresnick GH, Lebovitz RM, Appen RE, Gilbert-Barness EF, Pauli RM. Spinocerebellar ataxia, hypogonadotropic hypogonadism, and choroidal dystrophy (Boucher-Neuhauser syndrome). Am J Med Genet. 1989;33:409–14. [PubMed: 2801777]

McLennan K, Jeske Y, Cotterill A, Cowley D, Penfold J, Jones T, Howard N, Thomsett M, Choong C. Combined pituitary hormone deficiency in Australian children: clinical and genetic correlates. Clin Endocrinol (Oxf). 2003;58:785–94. [PubMed: 12780757]

Mendonca BB, Osorio MG, Latronico AC, Estefan V, Lo LS, Arnhold IJ. Longitudinal hormonal and pituitary imaging changes in two females with combined pituitary hormone deficiency due to deletion of A301,G302 in the PROP1 gene. J Clin Endocrinol Metab. 1999;84:942–5. [PubMed: 10084575]

Neuhauser G, Opitz JM. Autosomal recessive syndrome of cerebellar ataxia and hypogonadotropic hypogonadism. Clin Genet. 1975;7:426–34. [PubMed: 1149314]

Paracchini R, Giordano M, Corrias A, Mellone S, Matarazzo P, Bellone J, Momigliano-Richiardi P, Bona G. Two new PROP1 gene mutations responsible for compound pituitary hormone deficiency. Clin Genet. 2003;64:142–7. [PubMed: 12859410]

Park JK, Ozata M, Chorich LP, Cheng L, Bick DP, Sherins RJ, Ozdemir IC, Bolu E, Cogan JD, Phillips JA, Layman LC. Analysis of the PROP1 gene in a large cohort of patients with idiopathic hypogonadotropic hypogonadism. Clin Endocrinol (Oxf). 2004;60:147–9. [PubMed: 14678304]

Parks JS, Tenore A, Bongiovanni AM, Kirkland RT. Familial hypopituitarism with large sella turcica. N Engl J Med. 1978;298:698–702. [PubMed: 628396]

Phillips JA III. Inherited defects in growth hormone synthesis and action. In: Scriver CR, Beaudet AL, Sly WS, Valle D (eds) The Metabolic Basis of Inherited Disease, 6 ed. McGraw-Hill, New York, pp 3023-44. 1995

Rainbow LA, Rees SA, Shaikh MG, Shaw NJ, Cole T, Barrett TG, Kirk JM. Mutation analysis of POUF-1, PROP-1 and HESX-1 show low frequency of mutations in children with sporadic forms of combined pituitary hormone deficiency and septo-optic dysplasia. Clin Endocrinol (Oxf). 2005;62:163–8. [PubMed: 15670191]

Ranke MB. Growth hormone therapy in children: when to stop? Horm Res. 1995;43:122–5. [PubMed: 7750910]

Reynaud R, Barlier A, Vallette-Kasic S, Saveanu A, Guillet MP, Simonin G, Enjalbert A, Valensi P, Brue T. An uncommon phenotype with familial central hypogonadism caused by a novel PROP1 gene mutant truncated in the transactivation domain. J Clin Endocrinol Metab. 2005;90:4880–7. [PubMed: 15941866]

Reynaud R, Chadli-Chaieb M, Vallette-Kasic S, Barlier A, Sarles J, Pellegrini-Bouiller I, Enjalbert A, Chaieb L, Brue T. A familial form of congenital hypopituitarism due to a PROP1 mutation in a large kindred: phenotypic and in vitro functional studies. J Clin Endocrinol Metab. 2004;89:5779–86. [PubMed: 15531542]

Reynaud R, Saveanu A, Barlier A, Enjalbert A, Brue T. Pituitary hormone deficiencies due to transcription factor gene alterations. Growth Horm IGF Res. 2004;14:442–8. [PubMed: 15519252]

Riepe FG, Partsch CJ, Blankenstein O, Monig H, Pfaffle RW, Sippell WG. Longitudinal imaging reveals pituitary enlargement preceding hypoplasia in two brothers with combined pituitary hormone deficiency attributable to PROP1 mutation. J Clin Endocrinol Metab. 2001;86:4353–7. [PubMed: 11549674]

Rimoin DL, Phillips JA III. Genetic disorders of the pituitary gland. In: Rimoin DL, Connor JM, Pyeritz RE (eds) Principles and Practice of Medical Genetics, 3 ed. Churchill Livingstone, New York, pp 1331-64. 1997

Rosen T, Johannsson G, Johansson JO, Bengtsson BA. Consequences of growth hormone deficiency in adults and the benefits and risks of recombinant human growth hormone treatment. A review paper. Horm Res. 1995;43:93–9. [PubMed: 7721271]

Rosenfeld R. Disorders of growth hormone and insulin-like growth factor secretion and action. In: Pediatric Endocrinology, 1 ed. WB Saunders, Philadelpia. 1996

Siegel SF, Ahdab-Barmada M, Arslanian S, Foley TP Jr. Ectopic posterior pituitary tissue and paracentric inversion of the short arm of chromosome 1 in twins. Eur J Endocrinol. 1995;133:87–92. [PubMed: 7627343]

Tatsumi KI, Kikuchi K, Tsumura K, Amino N. A novel PROP1 gene mutation (157delA) in Japanese siblings with combined anterior pituitary hormone deficiency. Clin Endocrinol (Oxf). 2004;61:635–40. [PubMed: 15521968]

Turton JP, Mehta A, Raza J, Woods KS, Tiulpakov A, Cassar J, Chong K, Thomas PQ, Eunice M, Ammini AC, Bouloux PM, Starzyk J, Hindmarsh PC, Dattani MT. Mutations within the transcription factor PROP1 are rare in a cohort of patients with sporadic combined pituitary hormone deficiency (CPHD). Clin Endocrinol (Oxf). 2005;63:10–8. [PubMed: 15963055]

Voutetakis A, Argyropoulou M, Sertedaki A, Livadas S, Xekouki P, Maniati-Christidi M, Bossis I, Thalassinos N, Patronas N, Dacou-Voutetakis C. Pituitary magnetic resonance imaging in 15 patients with Prop1 gene mutations: pituitary enlargement may originate from the intermediate lobe. J Clin Endocrinol Metab. 2004;89:2200–6. [PubMed: 15126542]

Voutetakis A, Maniati-Christidi M, Kanaka-Gantenbein C, Dracopoulou M, Argyropoulou M, Livadas S, Dacou-Voutetakis C, Sertedaki A. Prolonged jaundice and hypothyroidism as the presenting symptoms in a neonate with a novel Prop1 gene mutation (Q83X). Eur J Endocrinol. 2004;150:257–64. [PubMed: 15012608]

Voutetakis A, Sertedaki A, Livadas S, Maniati-Christidi M, Mademtzis I, Bossis I, Dacou-Voutetakis C, Messinis IE. Ovulation induction and successful pregnancy outcome in two patients with Prop1 gene mutations. Fertil Steril. 2004;82:454–7. [PubMed: 15302300]

Wu W, Cogan JD, Pfaffle RW, Dasen JS, Frisch H, O'Connell SM, Flynn SE, Brown MR, Mullis PE, Parks JS, Phillips JA III, Rosenfeld MG. Mutations in PROP1 cause familial combined pituitary hormone deficiency. Nat Genet. 1998;18:147–9. [PubMed: 9462743]

Suggested Readings

Parks JS, Brown MR. Molecular basis of multiple pituitary hormone deficiency. In: Handwerger S (ed) Molecular and Cellular Pediatric Endocrinology. Humana Press Inc, Totowa, NJ, pp 297-307. 1999

Chapter Notes

Revision History

- 21 November 2005 (me) Comprehensive update posted to live Web site
- 16 June 2003 (ca) Comprehensive update posted to live Web site
- 7 December 2000 (me) Review posted to live Web site
- 18 October 1999 (jp) Original submission