GENEReviews

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Kallmann Syndrome

[*Includes: Kallmann Syndrome 1 (Kallmann Syndrome, X-Linked), Kallmann Syndrome 2, Kallmann Syndrome 3, Kallmann Syndrome 4*]

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Summary

Disease characteristics. Kallmann syndrome (KS) is characterized by the association of idiopathic or isolated hypogonadotropic hypogonadism (IHH) and anosmia (absent sense of smell). Infant boys often have micropenis and cryptorchidism. Adolescents and adults with IHH have clinical evidence of hypogonadism and incomplete sexual maturation on physical examination. Adult males with KS tend to have pre-pubertal testicular volume (i.e., <4 mL), absence of secondary sexual features (e.g., facial and axillary hair growth, deepening of the voice), increased muscle mass, diminished libido, erectile dysfunction, and infertility. Adult females have little or no breast development and primary amenorrhea. Body habitus is usually eunuchoidal with arm span exceeding height by 5 cm or more. Although skeletal maturation is delayed, the rate of linear growth is usually normal (except for the absence of a distinct pubertal growth spurt). Individuals with anosmia may or may not be aware of their olfactory deficiency. Additional findings can include synkinesia of the digits, unilateral renal agenesis, sensorineural hearing loss, cleft lip and/or palate, agenesis of one or more teeth, brachydactyly, syndactyly, and agenesis of the corpus callosum.

Diagnosis/testing. The diagnosis of KS is based on clinical findings, low or normal serum concentration of LH (luteinizing hormone) and FSH (follicle stimulating hormone) in the setting of low circulating concentrations of sex steroids, normal pituitary and hypothalamus on MRI, and absence of other hypothalamic or pituitary abnormalities. *KAL1*, *FGFR1*, *PROKR2*, and *PROK2* are the only genes known to be associated with KS. Together, mutations

in the four genes account for about 20%-25% of KS. Deletion of *KAL1* by FISH or array CGH (comparative genomic hybridization) is an extremely rare cause of KS. In 5%-10% of familial and simplex KS (i.e., a single occurrence in a family) sequence analysis identifies mutations in *KAL1*. Approximately 10% have mutations in *FGFR1*, approximately 5% in *PROKR2*, and fewer than 5% in *PROK2*. Such testing is clinically available.

Management. *Treatment of manifestations:* To induce and maintain secondary sex characteristics, gradually increasing doses of gonadal steroids (testosterone or hCG injections in males; estrogen and progestin in females); to stimulate spermatogenesis, either combined gonadotropin therapy [hCG and human menopausal gonadotropins (hMG) or recombinant FSH (rFSH)] or pulsatile GnRH therapy; to stimulate folliculogenesis, pulsatile GnRH therapy; in vitro fertilization is an option if spermatogenesis is achieved but infertility persists. *Surveillance:* At puberty, individuals diagnosed with KS in infancy or childhood need to have sexual maturation assessed by Tanner staging and measurement of serum concentrations of LH, FSH, and total testosterone (T) in males and estradiol (E_2) in females. Monitoring of bone mineral density should be considered. *Other:* Men using topical androgen replacement must take care to avoid exposing other individuals to treated skin.

Genetic counseling. Kallmann syndrome 1 (KS1), caused by mutations in *KAL1*, is inherited in an X-linked manner. KS2 (caused by mutations in *FGFR1*), KS3 (caused by mutations in *PROKR2*), and KS4 (caused by mutations in *PROK2*) are inherited in an autosomal dominant manner. In KS1, the father of an affected male will not have the disease nor will he be a carrier of the mutation. About 70% of males with KS1 are simplex cases (i.e., a single occurrence in a family). If the mother of the proband is a carrier, the chance of transmitting the disease-causing mutation in each pregnancy is 50%. Males who inherit the mutation will be affected; females who inherit the mutation will be carriers. Males with KS1 who are fertile will pass the disease-causing mutation to all of their daughters and none of their sons. Some individuals diagnosed with KS2, KS3, or KS4 have an affected parent; the proportion of cases caused by *de novo* mutations is unknown. Each child of an individual with KS2, KS3, or KS4 has a 50% chance of inheriting the mutation. Prenatal testing is possible for pregnancies at increased risk for KS1 or KS2 if the disease-causing mutation has been identified in an affected relative. Prenatal testing for KS3 and KS4 may be available through laboratories offering custom prenatal testing if the disease-causing mutation in the family is known.

Diagnosis

Clinical Diagnosis

Kallmann syndrome (KS) is the association of idiopathic or isolated hypogonadotropic hypogonadism (IHH) and anosmia (absent sense of smell).

IHH is diagnosed clinically by the presence of the following:

- **Clinical evidence of arrested sexual maturation or hypogonadism.** Absence of secondary sexual characteristics; diminished libido; infertility; amenorrhea in women; erectile dysfunction in men
- **Incomplete sexual maturation on physical examination** as determined by Tanner staging (Table 1)

Table 1. Tanner Staging

	I	II	III	IV	V
Pubic hair	None	Sparse hair that is long and slightly pigmented	Darker, coarser, curly hair	Adult hair covering pubis	Laterally distributed adult-type hair
Male genitalia	Childhood appearance of testes, scrotum, and penis (testicular volume <4 mL)	Enlargement of testes; reddish discoloration of scrotum	Continued growth of testes and elongation of penis	Continued growth of testes, widening of the penis with growth of the glans penis; scrotal darkening	Mature adult genitalia (testicular volume >15 mL)
Female breast development	No breast bud, small areola, slight elevation of papilla	Formation of the breast bud; areolar enlargement	Continued growth of the breast bud and areola; areola confluent with breast	Continued growth; areola and papilla form secondary mound projecting above breast contour	Mature (areola again confluent with breast contour; only papilla projects)

- Males with KS typically have Tanner stage I-II genitalia; females have Tanner stage I breasts; both males and females have Tanner stage II-III pubic hair since it is controlled in part by adrenal androgens.
- Men with KS often have pre-pubertal testicular volumes (<4mL).
- **Low or normal serum concentration of LH (luteinizing hormone) and FSH (follicle stimulating hormone) in the setting of low circulating concentrations of sex steroids** [total testosterone (T) <100 ng/dL in males and estradiol (E_2) <50 pg/mL in females]
- **Normal pituitary and hypothalamus on MRI.** MRI of the pituitary/olfactory region may indicate the absence of olfactory bulbs in individuals with KS and is needed to rule out secondary hypothalamic or pituitary causes of hormone deficiency.
- **No other hypothalamic or pituitary abnormalities**
- **Absence of other causes of hypogonadotropic hypogonadism.** See Hypogonadotropic Hypogonadism Overview.

Anosmia can be determined by history and confirmed using formal diagnostic smell tests, such as the University of Pennsylvania smell identification test (UPSIT) [Doty et al 1984]. This "scratch and sniff" test evaluates an individual's ability to identify 40 microencapsulated odorants and can be easily performed in most clinical settings.

Figure 1 differentiates the two types of IHH, Kallmann syndrome and normosmic IHH.

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.

Genes. *KAL1*, *FGFR1*, *PROKR2*, and *PROK2* are the only genes known to be associated with Kallmann syndrome (KS). Together, mutations in these genes account for about 20%-25% of KS.

Other loci. The gene(s) that account for the other 75%-80% of KS are unknown and unmapped.

Clinical testing

- ***KAL1* (Kallmann syndrome 1)**

FISH or deletion testing. Detection of deletion of *KAL1* by FISH or array CGH (comparative genomic hybridization) is possible [Hou et al 1999]; however, full deletions of *KAL1* are an extremely rare cause of KS.

Sequence analysis. Mutations in *KAL1* have been reported by several groups, making sequence analysis the favored approach for testing in individuals whose family history is highly suggestive of X-linked KS. In the authors' cohort of 250 individuals with IHH, approximately 5%-10% of familial and simplex (i.e., a single occurrence in a family) KS cases have been shown to have mutations in *KAL1* [Waldstreicher et al 1996, Oliveira et al 2001].

- ***FGFR1* (Kallmann syndrome 2)**

Sequence analysis. Mutations in *FGFR1* have been reported in several persons with autosomal dominant KS by a number of groups [Dode et al 2003; Sato et al 2004; Pitteloud, Acierno et al 2006; Pitteloud, Meysing et al 2006; Trarbach et al 2006]. In the authors' cohort of 250 individuals with IHH, approximately 10% have mutations in *FGFR1*. Unlike *KAL1*, disruption of which generally leads to a severe phenotype, mutations in *FGFR1* can have variable expressivity (see Genotype-phenotype Correlations).

- ***PROKR2* and *PROK2***

Sequence analysis. Recently, Dode et al (2006) reported several DNA sequence changes in the *PROKR2* and *PROK2* genes in persons with KS. Using sequence analysis in their research population, they found that approximately 5% of persons with KS had mutations in *PROKR2* and fewer than 5% had mutations in *PROK2*. However, as appropriate numbers of ethnically matched controls and biologic assays were not studied, further confirmation is required.

Table 2 summarizes molecular genetic testing for this disorder.

Table 2. Molecular Genetic Testing Used in Kallmann Syndrome

Test Method	Mutations Detected	Mutation Detection Frequency [1]	Test Availability
FISH	*KAL1* deletion	Rare	Clinical Testing
Sequence analysis	*KAL1* sequence variant	~5%-10%	
	FGFR1 sequence variant	~10%	Clinical Testing
	PROKR2 sequence variant	~5%	Clinical Testing
	PROK2 sequence variant	<5%	Clinical Testing

1. Proportion of affected individuals with a mutation(s) as classified by gene/locus, phenotype, population group, genetic mechanism, and/or test method

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

Testing Strategy

To establish the diagnosis of Kallmann syndrome (KS) in a proband. The clinical tests discussed in Molecular Genetic Testing can be offered to persons with findings of classic KS.

In familial KS cases, the mode of inheritance is useful in assessing the predictive value of the available tests:

- **X-linked pattern of inheritance.** Sequence analysis of the coding regions of *KAL1* may have higher yield than sequence analysis of *FGFR1*.
- **Autosomal dominant pattern of inheritance or for families with both anosmic IHH and normosmic IHH.** Testing of *FGFR1* may have higher yield than sequence analysis of *KAL1*.

For simplex KS cases:

- **Males.** Sequence analysis of the coding exons of *KAL1*, *FGFR1*, *PROKR2*, and *PROK2*
- **Females.** Sequence analysis of *FGFR1*, *PROKR2*, and *PROK2*

Carrier testing for relatives at-risk for Kallmann syndrome 1 requires identification of the disease-causing *KAL1* mutation in an affected family member.

Note: Carrier testing is relevant for an X-linked disorder but not for an autosomal dominant disorder.

Prenatal diagnosis for at-risk pregnancies requires prior identification of the disease-causing mutation in an affected family member.

Genetically Related (Allelic) Disorders

KAL1. Deletions in the terminal arm of Xp22.3 cause a contiguous gene syndrome including short stature, chondrodysplasia punctata, mental retardation, steroid sulfatase deficiency, and Kallmann syndrome [Ballabio et al 1989, Hou 2005].

FGFR1. In addition to KS with highly variable expressivity, the only other phenotype associated with mutations in *FGFR1* is Pfeiffer syndrome type 1. However, of the mutations that cause Pfeiffer syndrome, 95% occur in *FGFR2* and only 5% occur in *FGFR1*. (See *FGFR*-Related Craniosynostosis Syndromes.) Pfeiffer syndrome type 1 is characterized by coronal craniosynostosis with moderate-to-severe midface hypoplasia, usually normal intellect, broad and medially deviated thumbs and great toes with variable degree of brachydactyly. Hearing loss and hydrocephalus can be seen on occasion.

Clinical Description

Natural History

Gonadal function

- **Infancy.** Some individuals exhibit clues to the diagnosis of KS in early childhood. In boys, micropenis (stretched penile length <1.9 cm) and cryptorchidism are common features and can be associated with abnormally low serum concentrations of gonadotropins and testosterone in the first months of life.
- **Adolescence.** Individuals with KS display abnormal sexual maturation at puberty, usually with incomplete or absent development of secondary sexual characteristics.
- **Adulthood.** Adult males with KS tend to have pre-pubertal testicular volume (i.e., <4 mL), absence of secondary sexual features such as facial and axillary hair growth and deepening of the voice, and decreased muscle mass. Adult females have little or no breast development and primary amenorrhea. Since adrenal maturation proceeds normally, the low levels of androgens produced in the adrenal glands may allow normal onset of pubic hair growth (adrenarche) in both sexes.

Individuals with hypogonadotropic hypogonadism typically have a eunuchoidal body habitus with arm span exceeding height by 5 cm or more. Although skeletal maturation is delayed, the rate of linear growth is usually normal (except for the absence of a distinct pubertal growth spurt) [Van Dop et al 1987].

- **Fertile eunuch variant.** Not all individuals manifest the same severity of IHH and some individuals demonstrate some degree of pubertal development. This clinical variability is supported by analyses of the pulsatile pattern of gonadotropins in IHH, which demonstrate a spectrum of absent to arrested developmental patterns ranging from completely absent GnRH-induced LH pulses to sleep-entrained GnRH release that is indistinguishable from that of early puberty [Spratt et al 1987]. This variable level of endogenous GnRH activity permits spermatogenesis to occur with the potential to achieve fertility with little or no treatment [Smals et al 1978]. This extreme of the spectrum of abnormal pubertal development is referred to as the "fertile eunuch" phenotype of IHH. Although individuals with this syndrome exhibit clinical evidence of hypogonadism associated with low serum concentration of testosterone, they do have partial pubertal development with normal or near-normal testicular volumes.

Anosmia. Individuals with anosmia may or may not be aware of their olfactory deficiency; thus, formal testing is required to evaluate the ability to smell (see Diagnosis). Although family members sometimes comment on their relative's olfactory deficiency, the ability to smell is often culturally valued and may be down-played by the affected individual.

Other. The non-reproductive phenotypes in males with *KAL1* mutations include the following [Wegenke et al 1975, Quinton et al 2001, Massin et al 2003]:

- Synkinesia of the digits (present in approximately 80% of males with *KAL1* mutations). This can be demonstrated clinically by asking the individual to fully extend both arms and hands, and then move the fingers of one hand in isolation. The inability of the individual to move the fingers of one hand without exhibiting mirror movements of the digits of the other hand is synkinesia. An inability to play a musical instrument because of synkinesia is often obtained in the history.
- Unilateral renal agenesis (present in approximately 30% of males with *KAL1* mutations but also reported in persons with KS of unknown cause). This is often asymptomatic, and must be evaluated by ultrasound examination.
- Sensorineural hearing loss
- High-arched palate

The non-reproductive phenotypes caused by *FGFR1* mutations include the following [Dode et al 2003]:

- Synkinesia in about 10% of persons
- Cleft lip and/or palate
- Agenesis of one or more teeth
- Digit malformations (brachydactyly, syndactyly)
- Agenesis of the corpus callosum seen on MRI

Genotype-Phenotype Correlations

***KAL1* (Kallmann syndrome 1).** Males with a *KAL1* mutation generally have a severe reproductive phenotype. In frequent sampling studies using serum concentration of LH as a surrogate marker of GnRH secretion, males with *KAL1* mutations have complete absence of

GnRH pulsations. Males with *KAL1* mutations also have smaller testes at presentation and higher rates of cryptorchidism than males with normosmic IHH [Oliveira et al 2001; Pitteloud, Hayes, Boepple et al 2002].

***FGFR1* (Kallmann syndrome 2).** The IHH phenotype associated with *FGFR1* mutations often has variable expressivity within and across families with identical mutations. Absent puberty, partial puberty, or delayed puberty can be seen in individuals with the same mutation. Further, some persons with an *FGFR1* mutation are asymptomatic, denoting incomplete penetrance (see Penetrance). Thus, among individuals with the same *FGFR1* mutation in a family, some have an abnormal reproductive phenotype, while others do not [Pitteloud, Meysing et al 2006]. The IHH phenotype is more predominant in males with *FGFR1* mutations than in females.

Penetrance

Penetrance for the IHH phenotype is complete in males with *KAL1* mutations. Penetrance is incomplete in individuals with *FGFR1* mutations: individuals with normal gonadal function and an *FGFR1* mutation have been documented.

Penetrance for anosmia in men with mutations in *KAL1* is generally complete. In contrast, individuals with IHH and *FGFR1* mutations may be normosmic, hyposmic, or anosmic [Pitteloud, Acierno et al 2006].

Nomenclature

KS is a subset of idiopathic hypogonadotropic hypogonadism (IHH) and is sometimes referred to as anosmic IHH, hypogonadotropic hypogonadism and anosmia, or anosmic hypogonadism.

"Dysplasia olfactogenitalis of De Morsier" is a previously used term originating from an autopsy report describing 14 individuals with KS.

Prevalence

Estimates of the overall incidence of KS vary from approximately 1:10,000 to 1:86,000 [Seminara et al 1998].

One estimate of KS frequency utilized Sardinian conscripts. The overall incidence of testicular atrophy was 344 out of 600,000 (1:1174), although not all of the affected men could be investigated to determine the cause. Seven of the 265 men examined were anosmic, leading the authors to conclude that the incidence of KS was 1:86,000 men [Filippi 1986].

One study that assessed the incidence of KS in 24 individuals with anosmia found one previously undiagnosed case of KS, indicating that the incidence of KS may be high among individuals with anosmia [Pawlowitzki et al 1987].

In the authors' cohort of 250 individuals with IHH, the male predominance was significant, with a male-to-female ratio of nearly 4:1 [Seminara et al 1998]; approximately two-thirds of those with IHH have anosmia/hyposmia (Kallmann syndrome) and one-third have normosmic IHH (nIHH) [Authors, unpublished observation].

Differential Diagnosis

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

See Idopathic Hypogonadotropic Hypogonadism Overview.

Note testing algorithm to establish the diagnosis of idiopathic hypogonadotropic hypogonadism (Figure 2).

Management

Evaluations Following Initial Diagnosis

If a mutation in *KAL1* or *FGFR1* has been identified, appropriate initial clinical evaluation would include the following:

- Assessment of sexual maturation by Tanner stage (Table 1)
- Measurement of testicular volume in men
- Measurement of serum concentrations of LH, FSH, total testosterone (T) in men and estradiol (E_2) in women to determine the severity of GnRH deficit
- Assessment of non-reproductive phenotypes such as: severity of anosmia, presence of unilateral renal agenesis, synkinesia and/or skeletal abnormalities, agenesis of the corpus callosum (as seen on MRI)

Treatment of Manifestations

Treatment options for individuals with IHH include sex steroids, gonadotropin therapy, or pulsatile GnRH administration. Choice of therapy is determined by the goal(s) of treatment, i.e., to induce and maintain secondary sex characteristics and/or to bring about fertility.

Sex Steroid Replacement—As the majority of individuals with HH have not progressed through puberty, one of the initial challenges is initiation of the process of sexual maturation. When fertility is not immediately desired, replacement with gonadal steroids is the most practical option. Initial therapy should be started at low doses and gradually increased with the development of secondary characteristics.

For males with IHH/KS

- **Testosterone replacement.** In boys or men with prepubertal features, normal virilization can be effectively achieved with testosterone replacement.
  - Usual starting doses are 25-50 mg of a long-acting testosterone ester given intramuscularly every two weeks.
  - The doses can be gradually increased by 25-50 mg every two to three months until full virilization is achieved.
  - Once adult doses (~200 mg every two weeks) are reached, further adjustments are based on serum testosterone concentration.
  - Therapy should be continued indefinitely to ensure normal sexual function and maintenance of proper muscle, bone, and red blood cell mass.
  - Transdermal methods of testosterone administration can also be used; they have the added benefit of offering a more favorable pharmacokinetic profile.
- **Human chorionic gonadotropin (hCG) injections.** Although treatment with hCG can also promote testicular growth, this must be weighed against the increased risk of developing gynecomastia [Schopohl 1993]. Ultimately, the determination of which formulation to choose is based on the preference of the affected individual. Treatment with hCG is usually initiated at 1,000 IU intramuscularly or subcutaneously every other day to normalize serum testosterone concentration. Depending on the initial

testicular volume, some males with IHH can produce sufficient sperm to achieve conception with hCG treatment only [Burris et al 1988] (see Fertility Induction).

For females with IHH/KS. Initial treatment should consist of unopposed estrogen to allow optimal breast development. After approximately six months, once breast development has been optimized, a progestin should be added for endometrial protection.

Many formulations of estrogens and progestins are available and can be given in either cyclical or continuous fashion. Preference of the individual is important in choosing the right treatment plan, although low estrogen formulations should be considered in women with clotting abnormalities (see Factor V Leiden Thrombophilia and Prothrombin Thrombophilia).

Fertility Induction—For males with IHH. Although androgen administration helps maintain normal sexual function, gonadotropins are usually required to realize the fertility potential in males with HH/KS.

- **Gonadotropin therapy.** Traditionally, the combination of the gonadotropins hCG and human menopausal gonadotropins (hMG) or recombinant FSH (rFSH) is utilized to stimulate spermatogenesis. Treatment with hCG is usually initiated at 1,000 IU intramuscularly or subcutaneously every other day to normalize serum testosterone concentration. FSH is added to the regimen at doses ranging from 37.5 to 75 IU as either hMG or recombinant formulation. Depending on the initial testicular volume, some males with IHH can produce sufficient sperm to achieve conception with hCG treatment alone [Burris et al 1988]. However, if after six to nine months, semen analysis reveals persistent azoospermia or marked oligospermia, FSH is added to the regimen at doses ranging from 37.5 to 75 IU as either hMG or recombinant formulation.

  Care must be taken to track testicular volume, as this is one of the primary determinants of successful spermatogenesis. In fact, sperm are rarely seen in the semen analysis until testicular volume reaches 8 mL [Whitcomb & Crowley 1990]. In individuals without a history of cryptorchidism, sperm function is usually normal and conception can occur even with relatively low sperm counts.

- **Pulsatile GnRH stimulation.** An alternative method for induction of spermatogenesis is pulsatile GnRH. As the primary defect of IHH/KS is typically localized to the hypothalamus, the pituitary responds appropriately to physiologic doses of GnRH.

  Subcutaneous administration of GnRH in a pulsatile manner through a portable pump that delivers a GnRH bolus every two hours is an efficient way of inducing testicular growth and spermatogenesis [Whitcomb & Crowley 1990; Pitteloud, Hayes, Dwyer et al 2002]. Although gonadotropin therapy or pulsatile GnRH stimulation can induce spermatogenesis in approximately 90%-95% of men with IHH, some men have a better response to pulsatile GnRH stimulation than to gonadotropin therapy. However, pulsatile GnRH therapy is not currently approved by the Food and Drug Administration (FDA) for the treatment of infertility in men and thus is only available for treatment of infertility in men at specialized research centers.

  Successful spermatogenesis can be obtained in most males with IHH through pulsatile GnRH therapy or combined gonadotropin therapy. Men with IHH usually do not have a defect in sperm function; thus, low sperm numbers can often result in conception. However, if infertility remains a problem despite successful spermatogenesis, in vitro fertilization is an option.

For females with HH

- **Pulsatile GnRH stimulation and exogenous gonadotropins.** Pulsatile GnRH stimulation is an FDA-approved therapy for folliculogenesis in women with HH. Intravenous administration of GnRH at various frequencies throughout the menstrual cycle closely mimics normal cycle dynamics with the resulting ovulation of a single follicle [Santoro et al 1986]. This therapy offers a clear advantage over the traditional treatment with exogenous gonadotropins, which involves higher rates of both multiple gestation and ovarian hyperstimulation syndrome. For either approach, however, the rate of conception is approximately 30% per ovulatory cycle [Martin et al 1990].

Surveillance

Gonadal function. Individuals diagnosed with KS in infancy or childhood need to be evaluated at puberty as follows:

- Assessment of sexual maturation by Tanner staging (Table 1) and, in men, testicular volume
- Measurement of serum concentration of LH and FSH; total testosterone (T) in males and estradiol (E_2) in females

Bone mineral density. In addition to treating hypogonadism, the potential deterioration in bone health that may have resulted from periods of low circulating sex hormones should be addressed. Depending on the timing of puberty, duration of hypogonadism, and other osteoporotic risk factors (e.g., glucocorticoid excess, smoking) a bone mineral density study should be considered. Specific treatment for decreased bone mass should be considered depending on the degree of bone mineralization.

Agents/Circumstances to Avoid

When using topical androgen replacement in men, care must be taken to avoid exposure of treated skin to other individuals in the household. Anecdotal reports suggest that the transmission of clinically effective levels of testosterone from the patient to other family members, including women and children, is possible.

Testing of Relatives at Risk

Testing at-risk relatives may be indicated when a mutation has been identified in a family (e.g., testing the brother of a proband with a known *KAL1* mutation whose mother is a known carrier). Because of variable expressivity, however, it is unknown if a pre-pubertal child with a known mutation will progress through puberty in a normal or delayed fashion, or not at all. Therefore, hormone treatment should only be initiated when IHH is diagnosed with impaired pubertal development.

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

Therapies Under Investigation

Search ClinicalTrials.gov 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.

Other

Genetics clinics, staffed by genetics professionals, provide 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 may include disease-specific and/or umbrella support organizations.

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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

Kallmann syndrome 1 (caused by mutations in *KAL1*) is inherited in an X-linked manner.

Kallmann syndrome 2 (caused by mutations in *FGFR1*), Kallmann syndrome 3 (caused by mutations in *PROKR2*), and Kallmann syndrome 4 (caused by mutations in *PROK2*) are inherited in an autosomal dominant manner.

Risk to Family Members — X-Linked Inheritance

Parents of a proband

- The father of an affected male will not have the disease nor will he be a carrier of the mutation.
- In a family with more than one affected individual, the mother of an affected male is an obligate carrier.
- If pedigree analysis reveals that the proband is the only affected family member, the mother may be a carrier or the affected male may have a *de novo* gene mutation and, thus, the mother is not a carrier. The frequency of *de novo* mutations is unknown.
- If a woman has more than one affected son and the disease-causing mutation cannot be detected in her DNA, she may have germline mosaicism. Germline mosaicism in mothers has not been reported, but the possibility exists.
- Pedigree analysis reveals that about 70% of affected males are simplex cases (i.e., a single occurrence in a family).
- When an affected male is the only affected individual in the family, several possibilities regarding his mother's carrier status need to be considered:
  - He has a *de novo* disease-causing mutation in the *KAL1* gene and his mother is not a carrier.

- His mother is a carrier and has a *de novo* disease-causing mutation in the *KAL1* gene, either a) as a "germline mutation" (i.e., present at the time of her conception and therefore in every cell of her body); or b) as "germline mosaicism" (i.e., present only in some of her cells, including germ cells).
- His mother is a carrier and has a disease-causing mutation that she inherited from her parents, most commonly from maternal transmission.

Sibs of a proband

- The risk to sibs depends upon the carrier status of the mother.
- If the mother of the proband has a disease-causing mutation, the chance of transmitting it in each pregnancy is 50%. Male sibs who inherit the mutation will be affected; female sibs who inherit the mutation will be carriers.
- If the disease-causing mutation cannot be detected in the DNA of the mother of a simplex male, the risk to sibs is low but greater than that of the general population because of the possibility of germline mosaicism.

Offspring of a proband

- With appropriate treatment, males with Kallmann syndrome can be fertile.
- Males with X-linked Kallmann syndrome will pass the disease-causing mutation to all of their daughters and none of their sons.

Other family members of a proband. The proband's maternal uncles may be at risk of being affected and the maternal aunts may be at risk of being carriers. The aunts' offspring, depending upon their gender, may be at risk of being carriers or of being affected.

Carrier Detection

Carrier testing of at-risk female relatives is available on a clinical basis if the mutation has been identified in the family.

Risk to Family Members — Autosomal Dominant Inheritance

Parents of a proband

- Some individuals diagnosed with Kallmann syndrome 2, 3, or 4 have an affected parent, although the severity of the phenotype can differ.
- A proband with Kallmann syndrome 2, 3, or 4 may have the disorder as the result of a new gene mutation. The proportion of cases caused by *de novo* mutations is unknown.
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* mutation include: (1) a detailed pubertal history of both parents and (2) *FGFR1*, *PROKR2*, or *PROK2* sequence analysis of both parents. Evaluation of parents may determine that one is affected but has escaped previous diagnosis because of failure by health care professionals to recognize the syndrome and/or a milder phenotypic presentation. Therefore, an apparently negative family history cannot be fully confirmed until appropriate evaluations have been performed.

Note: Although some individuals diagnosed with Kallmann syndrome 2, 3, or 4 have an affected parent, the family history may appear to be negative because of failure to recognize the disorder in family members due to early death before the onset of symptoms, incomplete penetrance, or late onset of the disease in an affected relative.

Sibs of a proband

- The risk to the sibs of the proband depends upon the genetic status of the proband's parents.
- If a parent of the proband is affected, the risk to the sibs is 50% although the manifestations may be variable.
- When the parents are clinically unaffected, the risk to the sibs of a proband appears to be low.
- If the disease causing mutation found in the proband cannot be detected in the DNA of either parent, the risk to sibs is low, but greater than that of the general population because of the possibility of germline mosaicism. Although no instances of germline mosaicism have been reported, it remains a possibility.

Offspring of a proband. Each child of an individual with Kallmann syndrome 2, 3, or 4 has a 50% chance of inheriting the mutation.

Other family members of a proband. The risk to other family members depends upon the status of the proband's parents. If a parent is found to be affected, his or her family members may be at risk.

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 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 testing is possible for pregnancies of women who are carriers of a *KAL1* mutation. The usual procedure is to determine fetal sex by performing chromosome analysis on fetal cells obtained by chorionic villus sampling (CVS) at about ten to 12 weeks' gestation or by amniocentesis usually performed at about 15-18 weeks' gestation. If the karyotype is 46,XY, DNA from fetal cells can be analyzed for the known *KAL1* disease-causing mutation.

Prenatal diagnosis for pregnancies at increased risk for Kallmann syndrome 2 (caused by *FGFR1* mutations) 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 ten to 12 weeks' gestation. The disease-causing *FGFR1* allele of an affected family member must be identified before prenatal testing can be performed.

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

No laboratories offering molecular genetic testing for prenatal diagnosis of Kallmann syndrome 3 or 4 (caused by mutations in *PROKR2* and *PROK2*, respectively) are listed in the GeneTests Laboratory Directory. However, prenatal testing may be available for families in which the disease-causing mutation has been identified. For laboratories offering custom prenatal testing, see 

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Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutations have been identified. 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 Kallmann Syndrome

Gene Symbol	Chromosomal Locus	Protein Name
FGFR1	8p11.2-p11.1	Basic fibroblast growth factor receptor 1
KAL1	Xp22.3	Anosmin-1
PROK2	3p21.1	Prokineticin-2
PROKR2	20p13	Prokineticin receptor 2

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 Kallmann Syndrome

136350	FIBROBLAST GROWTH FACTOR RECEPTOR 1; FGFR1
147950	KALLMANN SYNDROME 2; KAL2
244200	KALLMANN SYNDROME 3; KAL3
308700	KALLMANN SYNDROME 1; KAL1
607002	PROKINETICIN 2; PROK2
607123	PROKINETICIN RECEPTOR 2; PROKR2
610628	KALLMANN SYNDROME 4; KAL4

Table C. Genomic Databases for Kallmann Syndrome

Gene Symbol	Entrez Gene	HGMD
FGFR1	2260 (MIM No. 136350)	FGFR1
KAL1	3730 (MIM No. 308700)	KAL1
PROK2	60675 (MIM No. 607002)	
PROKR2	128674 (MIM No. 607123)	

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

Molecular Genetic Pathogenesis

Anosmia results because the olfactory axons and GnRH-secreting neurons depend on each other to migrate to the brain from the olfactory placode during development. Defects in this migration result in the co-development of GnRH deficiency and anosmia.

KAL1

Normal allelic variants: *KAL1* has 14 exons

Pathologic allelic variants: Reported pathologic mutations in *KAL1* include deletion of the entire gene, deletion of several nucleotides, missense mutations, nonsense mutations, and mutations predicted to cause splice variants.

For more information, see Genomic Databases table.

Normal gene product: The protein encoded by *KAL1*, also known as anosmin, has 680 amino acids with functional similarities with molecules involved in neural development [Rugarli et al 1993]. The N-terminus domains share homologies with a consensus sequence of the whey acid protein family and a motif found in protease inhibitors. The C terminus contains a series of fibronectin type III repeats similar to those found in neural cell adhesion molecules.

Abnormal gene product: Impaired function of anosmin results in a migratory defect of the olfactory and GnRH neurons from the olfactory placode during development [Cariboni et al 2004]. The obstructed migration of these neurons accounts for the tell-tale symptoms of KS, IHH, and anosmia, and leads to olfactory bulb malformation detectable by MRI in the majority of individuals.

FGFR1

Normal allelic variants: *FGFR1* has 18 exons with a known splice variant at the end of exon 10.

Pathologic allelic variants: Pathologic mutations in *FGFR1* include deletions, missense, nonsense, and splice variant mutations.

For more information, see Genomic Databases table.

Normal gene product: The *FGFR1* gene encodes a membrane receptor with three extracellular immunoglobulin-like domains and an intracellular tyrosine kinase domain [Lee et al 1989]. Ligand binding results in receptor dimerization and recruitment of intracellular signaling proteins.

Abnormal gene product: Abnormal *FGFR1* gene products result in impaired receptor signaling. The gene dose effect of anosmin and its interaction with *FGFR1* in guiding GnRH neuronal migration have been proposed as explanations for the greater predominance of the IHH phenotype in males than females [Dode et al 2003].

PROKR2

Normal allelic variants: *PROKR2* has two exons.

Pathologic allelic variants: Pathologic variants of *PROKR2* described include missense and nonsense mutations.

Normal gene product: The normal gene product encodes the prokineticin receptor 2, a G protein-coupled transmembrane receptor for PROK2.

Abnormal gene product: Functional effects of mutations identified in humans are unknown. Knockout mice lack olfactory bulbs and have severe atrophia of the reproductive system related to the absence of gonadotropin-releasing hormone-synthesizing neurons in the hypothalamus [Masumoto et al 2006].

PROK2

Normal allelic variants: *PROK2* has four coding exons, including an alternative exon 3.

Pathologic allelic variants: Pathologic variants of *PROK2* include missense and nonsense mutations, as well as alterations of translation start sites.

Normal gene product: The normal gene product is prokineticin-2, the main ligand of PROKR2.

Abnormal gene product: The functional effects of mutations identified in humans are unknown.

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.

The Pituitary Foundation
PO Box 1944
Bristol BS99 2UB
United Kingdom
Email: helpline@pituitary.org.uk
Kallmann's Syndrome

Medline Plus
Hypogonadotropic hypogonadism

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

Ballabio A, Bardoni B, Carrozzo R, Andria G, Bick D, Campbell L, Hamel B, Ferguson-Smith MA, Gimelli G, Fraccaro M, et al. Contiguous gene syndromes due to deletions in the distal short arm of the human X chromosome. Proc Natl Acad Sci U S A. 1989;86:10001–5. [PubMed: 2602357]

Burris AS, Rodbard HW, Winters SJ, Sherins RJ. Gonadotropin therapy in men with isolated hypogonadotropic hypogonadism: the response to human chorionic gonadotropin is predicted by initial testicular size. J Clin Endocrinol Metab. 1988;66:1144–51. [PubMed: 3372679]

Cariboni A, Pimpinelli F, Colamarino S, Zaninetti R, Piccolella M, Rumio C, Piva F, Rugarli EI, Maggi R. The product of X-linked Kallmann's syndrome gene (KAL1) affects the migratory activity of gonadotropin-releasing hormone (GnRH)-producing neurons. Hum Mol Genet. 2004;13:2781–91. [PubMed: 15471890]

Dode C, Levilliers J, Dupont JM, De Paepe A, Le Du N, Soussi-Yanicostas N, Coimbra RS, Delmaghani S, Compain-Nouaille S, Baverel F, Pecheux C, Le Tessier D, Cruaud C, Delpech M, Speleman F, Vermeulen S, Amalfitano A, Bachelot Y, Bouchard P, Cabrol S, Carel JC, Delemarre-van de Waal H, Goulet-Salmon B, Kottler ML, Richard O, Sanchez-Franco F, Saura R, Young J, Petit C, Hardelin JP. Loss-of-function mutations in FGFR1 cause autosomal dominant Kallmann syndrome. Nat Genet. 2003;33:463–5. [PubMed: 12627230]

Dode C, Teixeira L, Levilliers J, et al. Kallmann syndrome: mutations in the genes encoding prokineticin-2 and prokineticin receptor-2. PLoS Genet. 2006;2:e175. [PubMed: 17054399]

Doty RL, Shaman P, Kimmelman CP, Dann MS. University of Pennsylvania smell identification test: a rapid quantitative olfactory function test for the clinic. Laryngoscope. 1984;94:176–8. [PubMed: 6694486]

Filippi G. Klinefelter's syndrome in Sardinia. Clinical report of 265 hypogonadic males detected at the time of military check-up. Clin Genet. 1986;30:276–84. [PubMed: 3791676]

Hou JW. Detection of gene deletions in children with chondrodysplasia punctata, ichthyosis, Kallmann syndrome, and ocular albinism by FISH studies. Chang Gung Med J. 2005;28:643–50. [PubMed: 16323556]

Hou JW, Tsai WY, Wang TR. Detection of KAL-1 gene deletion with fluorescence in situ hybridization. J Formos Med Assoc. 1999;98:448–51. [PubMed: 10443071]

Lee PL, Johnson DE, Cousens LS, Fried VA, Williams LT. Purification and complementary DNA cloning of a receptor for basic fibroblast growth factor. Science. 1989;245:57–60. [PubMed: 2544996]

Martin K, Santoro N, Hall J, Filicori M, Wierman M, Crowley WF Jr. Clinical review 15: Management of ovulatory disorders with pulsatile gonadotropin-releasing hormone. J Clin Endocrinol Metab. 1990;71:1081A–G. [PubMed: 2229271]

Massin N, Pecheux C, Eloit C, Bensimon JL, Galey J, Kuttenn F, Hardelin JP, Dode C, Touraine P. X chromosome-linked Kallmann syndrome: clinical heterogeneity in three siblings carrying an intragenic deletion of the KAL-1 gene. J Clin Endocrinol Metab. 2003;88:2003–8. [PubMed: 12727945]

Matsumoto S, Yamazaki C, Masumoto KH, Nagano M, Naito M, Soga T, Hiyama H, Matsumoto M, Takasaki J, Kamohara M, Matsuo A, Ishii H, Kobori M, Katoh M, Matsushime H, Furuichi K, Shigeyoshi Y. Abnormal development of the olfactory bulb and reproductive system in mice lacking prokineticin receptor PKR2. Proc Natl Acad Sci U S A. 2006;103:4140–5. [PubMed: 16537498]

Oliveira LM, Seminara SB, Beranova M, Hayes FJ, Valkenburgh SB, Schipani E, Costa EM, Latronico AC, Crowley WF Jr, Vallejo M. The importance of autosomal genes in Kallmann syndrome: genotype-phenotype correlations and neuroendocrine characteristics. J Clin Endocrinol Metab. 2001;86:1532–8. [PubMed: 11297579]

Pawlowitzki IH, Diekstall P, Schadel A, Miny P. Estimating frequency of Kallmann syndrome among hypogonadic and among anosmic patients. Am J Med Genet. 1987;26:473–9. [PubMed: 3101500]

Pitteloud N, Acierno JS Jr, Meysing A, Eliseenkova AV, Ma J, Ibrahimi OA, Metzger DL, Hayes FJ, Dwyer AA, Hughes VA, Yialamas M, Hall JE, Grant E, Mohammadi M, Crowley WF Jr. Mutations in fibroblast growth factor receptor 1 cause both Kallmann syndrome and normosmic idiopathic hypogonadotropic hypogonadism. Proc Natl Acad Sci U S A. 2006;103:6281–6. [PubMed: 16606836]

Pitteloud N, Hayes FJ, Boepple PA, DeCruz S, Seminara SB, MacLaughlin DT, Crowley WF Jr. The role of prior pubertal development, biochemical markers of testicular maturation, and genetics in elucidating the phenotypic heterogeneity of idiopathic hypogonadotropic hypogonadism. J Clin Endocrinol Metab. 2002;87:152–60. [PubMed: 11788640]

Pitteloud N, Hayes FJ, Dwyer A, Boepple PA, Lee H, Crowley WF Jr. Predictors of outcome of long-term GnRH therapy in men with idiopathic hypogonadotropic hypogonadism. J Clin Endocrinol Metab. 2002;87:4128–36. [PubMed: 12213860]

Pitteloud N, Meysing A, Quinton R, Acierno JS Jr, Dwyer AA, Plummer L, Fliers E, Boepple P, Hayes F, Seminara S, Hughes VA, Ma J, Bouloux P, Mohammadi M, Crowley WF Jr. Mutations in fibroblast growth factor receptor 1 cause Kallmann syndrome with a wide spectrum of reproductive phenotypes. Mol Cell Endocrinol. 2006;254-255:60–9. [PubMed: 16764984]

Quinton R, Duke VM, Robertson A, et al. Idiopathic gonadotrophin deficiency: genetic questions addressed through phenotypic characterization. Clin Endocrinol (Oxf). 2001;55:163–74. [PubMed: 11531922]

Rugarli EI, Lutz B, Kuratani SC, Wawersik S, Borsani G, Ballabio A, Eichele G. Expression pattern of the Kallmann syndrome gene in the olfactory system suggests a role in neuronal targeting. Nat Genet. 1993;4:19–26. [PubMed: 8513320]

Santoro N, Filicori M, Crowley WF Jr. Hypogonadotropic disorders in men and women: diagnosis and therapy with pulsatile gonadotropin-releasing hormone. Endocr Rev. 1986;7:11–23. [PubMed: 3082615]

Sato N, Katsumata N, Kagami M, Hasegawa T, Hori N, Kawakita S, Minowada S, Shimotsuka A, Shishiba Y, Yokozawa M, Yasuda T, Nagasaki K, Hasegawa D, Hasegawa Y, Tachibana K, Naiki Y, Horikawa R, Tanaka T, Ogata T. Clinical assessment and mutation analysis of Kallmann syndrome 1 (KAL1) and fibroblast growth factor receptor 1 (FGFR1, or KAL2) in five families and 18 sporadic patients. J Clin Endocrinol Metab. 2004;89:1079–88. [PubMed: 15001591]

Schopohl J. Pulsatile gonadotrophin releasing hormone versus gonadotrophin treatment of hypothalamic hypogonadism in males. Hum Reprod 8 Suppl. 1993;2:175–9. [PubMed: 8276954]

Seminara SB, Hayes FJ, Crowley WF Jr. Gonadotropin-releasing hormone deficiency in the human (idiopathic hypogonadotropic hypogonadism and Kallmann's syndrome): pathophysiological and genetic considerations. Endocr Rev. 1998;19:521–39. [PubMed: 9793755]

Smals AG, Kloppenborg PW, van Haelst UJ, Lequin R, Benraad TJ. Fertile eunuch syndrome versus classic hypogonadotrophic hypogonadism. Acta Endocrinol (Copenh). 1978;87:389–99. [PubMed: 343467]

Spratt DI, Carr DB, Merriam GR, Scully RE, Rao PN, Crowley WF Jr. The spectrum of abnormal patterns of gonadotropin-releasing hormone secretion in men with idiopathic hypogonadotropic hypogonadism: clinical and laboratory correlations. J Clin Endocrinol Metab. 1987;64:283–91. [PubMed: 3098771]

Trarbach EB, Costa EM, Versiani B, de Castro M, Baptista MT, Garmes HM, de Mendonca BB, Latronico AC. Novel fibroblast growth factor receptor 1 mutations in patients with congenital hypogonadotropic hypogonadism with and without anosmia. J Clin Endocrinol Metab. 2006;91:4006–12. [PubMed: 16882753]

Van Dop C, Burstein S, Conte FA, Grumbach MM. Isolated gonadotropin deficiency in boys: clinical characteristics and growth. J Pediatr. 1987;111:684–92. [PubMed: 2889818]

Waldstreicher J, Seminara SB, Jameson JL, Geyer A, Nachtigall LB, Boepple PA, Holmes LB, Crowley WF Jr. The genetic and clinical heterogeneity of gonadotropin-releasing hormone deficiency in the human. J Clin Endocrinol Metab. 1996;81:4388–95. [PubMed: 8954047]

Wegenke JD, Uehling DT, Wear JB Jr, Gordon ES, Bargman JG, Deacon JS, Herrmann JP, Opitz JM. Familial Kallmann syndrome with unilateral renal aplasia. Clin Genet. 1975;7:368–81. [PubMed: 1080088]

Whitcomb RW, Crowley WF Jr. Clinical review 4: Diagnosis and treatment of isolated gonadotropin-releasing hormone deficiency in men. J Clin Endocrinol Metab. 1990;70:3–7. [PubMed: 2403572]

Suggested Readings

Ballabio A, Rugarli EI. Kallmann syndrome. In: Scriver CR, Beaudet AL, Sly WS, Valle D, Vogelstein B (eds) The Metabolic and Molecular Bases of Inherited Disease (OMMBID), McGraw-Hill, New York, Chap 225. www.ommbid.com. revised 2002

Chapter Notes

Revision History

- 23 May 2007 (me) Review posted to live Web site
- 1 June 2006 (jcp) Original submission

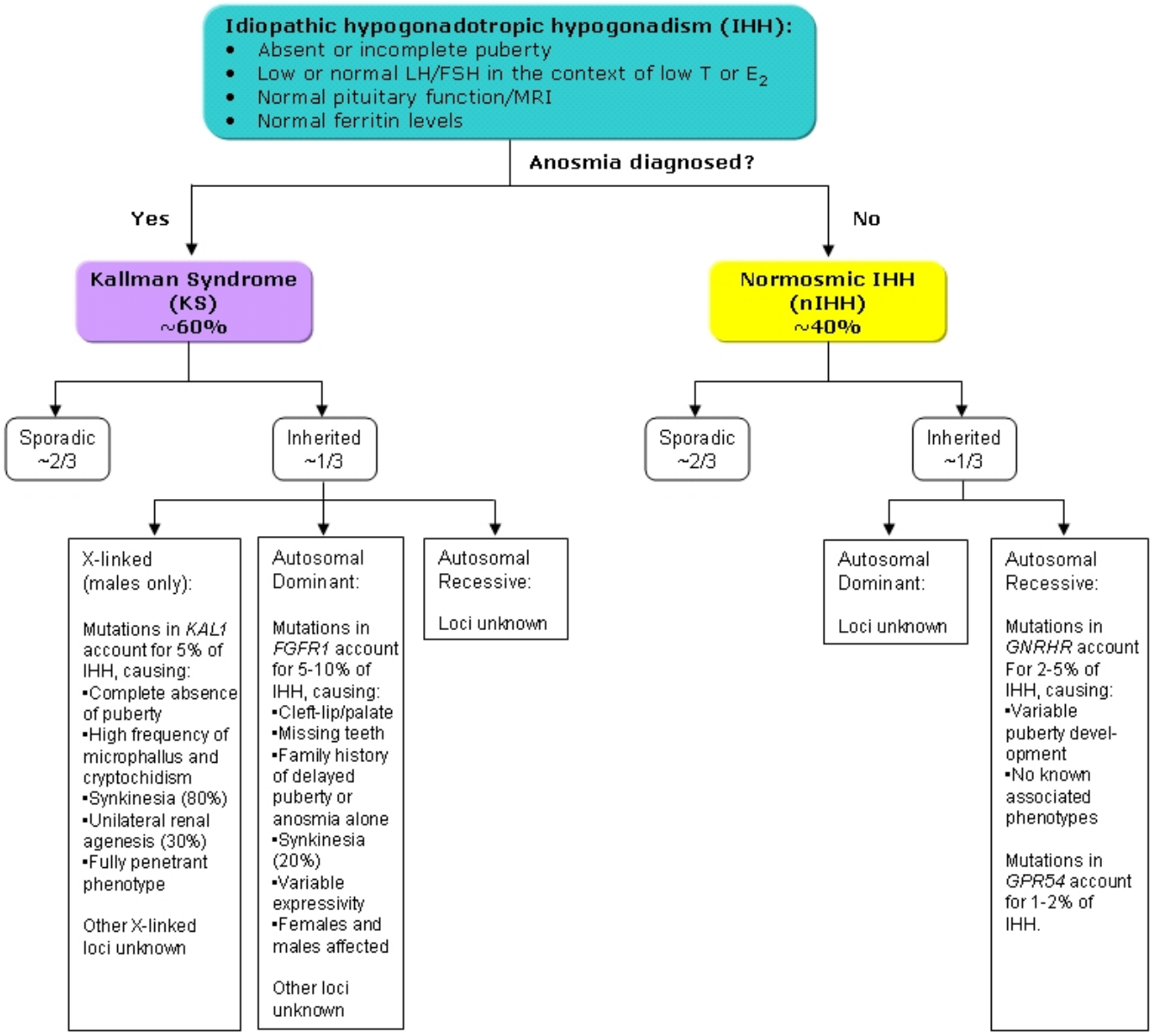

Figure 1. Types of idiopathic hypogonadotropic hypogonadism

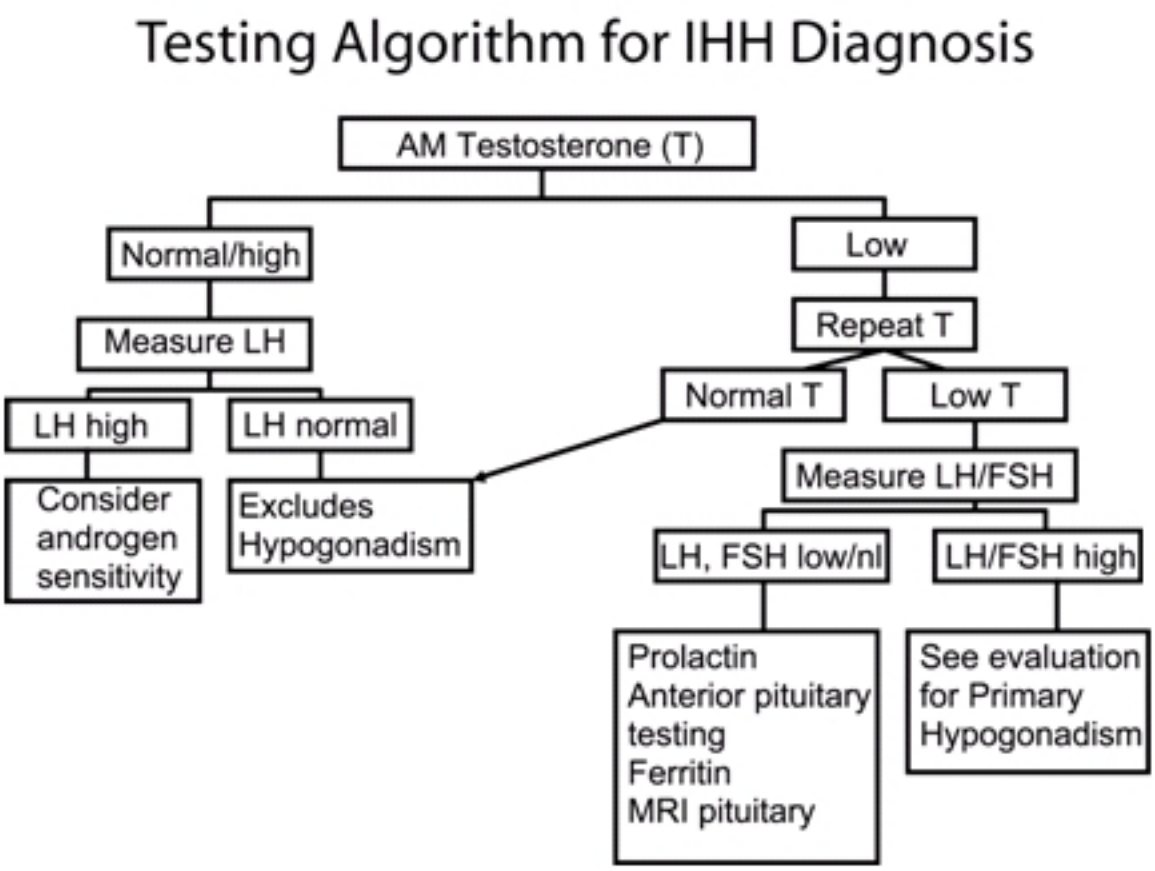

Figure 2. Testing algorithm to establish the diagnosis of idiopathic hypogonadotropic hypogonadism