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Genetic insights into human isolated gonadotropin deficiency

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Abstract The identification of naturally occurring genetic mutations has provided unique insight into the current knowledge of the human hypothalamic-pituitary-gonadal axis. In the past decade, several monogenic causes have been reported in patients with isolated gonadotropin deficiency. Kallmann Syndrome is a clinically and genetically heterogeneous disorder, characterized by isolated hypogonadotropic hypogonadism and anosmia or hyposmia. To date, loss-of-function mutations in the genes encoding anosmin-1 (*KAL1*) and fibroblast growth factor receptor 1 (*FGFR1*) have been described in the X-linked and autosomal dominant forms of this syndrome, respectively. More recently, several heterozygous, homozygous or compound heterozygous mutations in the G protein-coupled prokineticin receptor-2 *(PROKR2*) and one of its ligands, prokineticin-2 (*PROK2*) were described in Kallmann syndrome. In addition, complex genetic transmission (digenic inheritance) was recently demonstrated in this condition. Regarding isolated hypogonadotropic hypogonadism without olfactory abnormalities, loss-of-function mutations in the Gonadotropin-releasing hormone (GnRH) receptor (*GnRH-R*) or the G-protein coupled receptor 54 (*GPR54*) genes, both encoding transmembrane receptors, have been described, as well as FGFR1 mutations. Finally, mutations of the beta sub-units of LH and FSH have been described in patients with selective gonadotropin deficiency. We review the role of these distinct genetic factors in human isolated hypogonadotropic hypogonadism.

Keywords Hypogonadotropin hypogonadism · Kallman syndrome · Gonadotropin deficiency · Gonadotropin-releasing hormone

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Introduction

The episodic secretion of gonadotropin-releasing hormone (GnRH) from the hypothalamus is a key requirement for the initiation and maintenance of normal reproductive function. In humans, the hypothalamic-pituitary-gonadal axis is fully active in the neonatal life, followed by a period of quiescence during childhood and reactivation in the beginning of puberty. Several factors that trigger the resurgence of pulsatile GnRH secretion at puberty have been described [1].

Congenital isolated hypogonadotropic hypogonadism (IHH) is defined by low gonadal sex steroid plasma levels in the setting of low or normal pituitary secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH). It is characterized by complete or partial absence of endogenous GnRH-induced gonadotropin secretion, absence of anatomical abnormalities in the hypothalamic and pituitary region, and normal baseline and reserve testing of the remaining hypothalamic-pituitary axis [2]. IHH may occur in association with olfactory abnormalities (Kallmann syndrome), whereas a normal sense of smell defines normosmic IHH.

Kallmann syndrome is a clinically and genetically heterogeneous disorder, more prevalent in males (1:10,000)

than in females (1:50,000) [3]. Although sporadic cases are more frequent, families with Kallmann syndrome have been reported with X-linked, autosomal dominant or recessive modes of inheritance [4–6]. In the past decade, several monogenic causes of IHH have been identified. *KAL1* (Kallmann syndrome gene 1) and fibroblast growth factor receptor 1 (*FGFR1*) defects were associated with X-linked and autosomal Kallmann syndrome, respectively. More recently, several heterozygous, homozygous or compound heterozygous mutations in the G protein-coupled prokineticin receptor-2 (*PROKR2*) and one of its ligands, prokineticin-2 (*PROK2*), have been described in Kallmann syndrome. In addition, complex genetic transmission (digenic inheritance) was recently demonstrated in this condition. Mutations in the GnRH receptor (*GnRH-R*), G protein-coupled receptor-54 (*GPR54*) and its ligand kisspeptin are associated with normosmic IHH. In addition, selective hypogonadotropic hypogonadism due to mutations in the FSH beta and LH beta-subunit genes has been rarely reported.

KAL1 and X-linked Kallmann syndrome

Unlike most neurons in the brain, the origin of GnRH neurons lies outside the central nervous system, in the nasal placode of the embryonic nasal prominence, sharing a common origin and destiny with the olfactory neurons that migrate together across the cribiform plate toward the developing olfactory bulb [7, 8]. GnRH neurons subsequently disengage from their olfactory guidance fibers and further migrate to their ultimate destination in the medial hypothalamus [9]. Abnormalities in this migratory process explain the association of IHH and olfactory defects in patients with Kallmann syndrome [10, 11]. These abnormalities probably arise from impaired targeting and migration of the olfactory axons and of the GnRH secreting neurons [10, 11], or from alterations in the initial steps of olfactory bulb differentiation [12]. The migrational arrest of GnRH neurons within the meninges has been reported in a study of a 19-week human fetus with X-linked Kallmann syndrome [13]. Furthermore, olfactory bulb agenesis or hypoplasia has been detected by magnetic resonance imaging in some patients with this condition [14, 15].

Intragenic deletions and point mutations of *KAL1* gene, located at Xp22.3, are responsible for X-linked Kallmann syndrome [10, 11, 16]. Although incomplete penetrance of hypogonadism and/or anosmia within and across families with Kallmann syndrome is frequently described, patients with *KAL1* mutations exhibit an almost uniformly severe and highly penetrant reproductive phenotype [4, 17]. In addition, several non-reproductive and non-olfactory disorders are largely attributed to *KAL1* defects, including midline facial defects, such as cleft lip and/or palate, short metacarpals, renal agenesis [6, 18, 19], sensorineural hearing loss [6, 18, 20], bimanual synkinesia [20, 21], oculomotor abnormalities [6, 20] and cerebellar ataxia [20]. Renal agenesis and bimanual synkinesis show the highest incidences, occurring in approximately 30–40% and 75% of Kallmann syndrome cases, respectively [22].

KAL1 comprises 14 exons and encodes an extracellular protein of 680 amino acids, anosmin-1, which contains a cysteine-rich region, a whey acidic protein (WAP) domain, homologous to some serine protease inhibitors, four fibronectin-like type III (FnIII) repeats, structurally related to cell adhesion molecules, and several predicted heparin sulfate binding regions [10, 11]. Mutations in *KAL1* are distributed throughout the gene, although most of the point mutations cluster in the four FnIII repeat region of anosmin-1 [16]. These mutations have been identified in approximately 8–11% of the sporadic and in 14–50% of the familial cases of X-linked Kallmann, respectively [4, 23]. No correlation has been demonstrated between phenotype and location of the described mutations.

Experiments in vitro showed that anosmin-1 has a role in the control of different cell functions, including cell adhesion and neurite/axonal elongation and fasciculation, epithelial morphogenesis as well as in the migratory activity of GnRH-producing neurons [24–27]. Molecular modeling showed that anosmin-1 domains are highly extended and have intradomain flexibility, which account for the known ability of anosmin-1 to interact with macromolecular ligands in intracellular matrix [28]. However, the molecular mechanism of anosmin-1 action is widely unknown. It has been shown that the reduction of the number of FnIII repeats determines a weaker cell surface association and a lower heparan-sulfate binding affinity [29] and can produce a protein that completely lacks in vivo activity [30, 31]. Andrenacci et al. [31] performed a structure-function analysis of the different *Drosophila melanogaster* Kal-1 domains. This study suggests that the FnIII repeats have a main and specific role for the activity of the anosmin-1, while the WAP domain might have only a modulator role, strictly connected to that of the fibronectins. In addition, the functional relevance of these different domains was shown to be dependent on the extracellular context.

FGFR1 and autosomal dominant Kallmann syndrome

The *FGFR1* gene, also called *KAL2*, is located at chromosome 8p12 and comprises 18 exons. Dode et al. [32], studying two patients with contiguous gene syndrome due to interstitial deletions at chromosome 8p11.2–12, first reported the association of loss-of-function mutations in *FGFR1* with the dominant form of Kallmann syndrome. Since then, several *FGFR1* mutations, spanning all

functional domains of the receptor, have been identified in approximately 10–17% of Kallmann syndrome affected individuals [32–39]. Similar to *KAL1* defects, other non-reproductive and non-olfactory disorders are associated with Kallmann syndrome due to *FGFR1* defects, including cleft palate or lip, dental agenesis and bimanual synkinesis [32–35] (Table 1). To date, only two patients with *FGFR1* mutations and bimanual synkinesis [32, 35] have been identified; this clinical defect usually observed in *KAL1* patients.

FGFR1 abnormalities have been associated with wide variability of sexual maturation, as demonstrated by the presence of phenotypes that varied from complete absence of puberty to normal reproductive function within families harboring the same mutation [39]. Isolated anosmia has also been identified as a partial phenotypic manifestation of *FGFR1* mutations in familial cases of autosomal dominant Kallmann syndrome [35, 39].

In addition, *FGFR1* defects were recently implicated in a rare variant form of Kallmann syndrome, characterized by spontaneous reversibility of reproductive function [40] and more recently, in the etiology of IHH with normal olfaction [35, 41, 42]. These reports demonstrated that *FGFR1* mutations can cause distinct subtypes of IHH, suggesting that GnRH neuronal migratory defects in these cases are not always complete and variable degrees of endogenous GnRH secretion may occur [40].

The mature FGFR1 protein, one of the four transmembrane receptors for fibroblast growth factor (FGF) ligands, consists of three extracellular immuno-globulin-like loops, an acid box between the first two immunoglobulin loops, a transmembrane domain, and an intracellular split tyrosine kinase domain [43]. The FGFR1 signaling is achieved by receptor conformational changes upon ligand binding, leading to dimerization and subsequent activation by autophosphorylation of tyrosine kinase intracellular domains. Heparin or heparan sulfate proteoglycan (HSPG) binding is essential for the dimerization and activation of the FGF–FGFR complex [44, 45].

Several studies on the expression patterns of FGF ligands and receptors during the central nervous system development indicate the critical role of FGF in the initial generation of neural tissue [46]. This activity is also present in the rostral forebrain, directly affecting the olfactory bulb development, which could influence the GnRH neuronal migratory activity [47]. Therefore, loss-of-function mutations in *FGFR1* are thought to result in a defect in GnRH neuron migration via abnormal olfactory bulb morphogenesis [22]. Consistent with this hypothesis, olfactory bulb agenesis or hypoplasia has been detected by MRI in patients with *FGFR1* mutations [32, 34, 35, 40]. However, the mechanism and effects of loss-of-function *FGFR1* mutations are poorly understood. Structural and biochemical studies showed that some mutations in the tyrosine kinase and immunoglobulin II domains described in Kallmann syndrome patients reduced the tyrosine kinase activity of FGFR1 [41].

The clinical findings shared by *KAL1* and *FGFR1* mutated patients argue in favor of a putative anosmin-1 and FGFR1 interaction, and/or activation of common pathways. Dode and Hardelin [22] proposed that such interaction could explain the higher prevalence of Kallmann syndrome in males. Since *KAL1* gene escapes X-inactivation, a higher local concentration of anosmin-1 is expected in human females, which could compensate for a pathological situation of FGFR1 haploinsufficiency [22]. In fact, recent studies showed that anosmin-1 acts as a FGFR1-specific modulator and co-ligand through a heparan sulfate-dependent mechanism and amplifies the resulting downstream signaling responses [46]. Interaction of FGF2/FGFR1/anosmin-1 was also demonstrated in an experimental model of embryonic mouse optic nerve, suggesting that this system may be relevant in the context of demyelinating diseases [48]. However, the function of anosmin-1 in vivo and its connection with FGFR1 signaling are as yet unknown and several important issues remain unresolved.

Prokineticin Receptor-2 and its ligand

The gene *PROKR2*, encoding the prokineticin receptor-2, was considered as a potential causative gene of Kallmann syndrome. This fact was strongly suggested by the abnormal development of olfactory bulbs combined with severe atrophy of the reproductive system demonstrated in mutant mice lacking this G protein-coupled transmembrane receptor [49]. Indeed, very recently, Dode et al. [50] investigated 192 (144 males and 48 females) unrelated individuals affected by Kallmann syndrome and identified 10 different mutations of PROKR2 (one frameshift and nine missense mutations) in 14 patients with variable degrees of olfactory and reproductive dysfunction. These PROKR2 mutations were found in heterozygous (n = 10), homozygous (n = 2) or compound heterozygous (n = 2) cases. One of the patients, who carried a PROKR2 mutation in heterozygous state, also carried a missense mutation in *KAL1*, suggesting possible digenic inheritance of the disease [50]. In addition, 4 different heterozygous mutations were also identified in the main ligand of PROKR2 in patients affected by Kallmann syndrome. These mutations were located at highly conserved amino acids and the great majority was not found in the control group [50]. However, no functional studies of the PROKR2 and PROK2 mutations that could confirm the insufficient prokineticin-signaling has been performed so far.

Table 1 *FGFR1* mutations in Kallmann syndrome and normosmic IHH patients

Mutation	Nucleotide change	Localization (domain)	Inheritance	Phenotypes	References
G48S[a]	142G>A	IgI	sporadic	normal sense of smell	[35]
R78C	232C>G	IgI	familial	cryptorchidism	[39]
R78C	232C>G	IgI	sporadic	cryptorchidism, micropenis	[39]
G97D	290G>A	IgI	sporadic	–	[32]
Y99C	296A>G	IgI	sporadic	–	[32]
Frameshift	303–304insCC	IgI	sporadic	–	[32]
V102I	303G>A	IgI	familial	–	[33]
V102I	304G>A	IgI	sporadic	cryptorchidism, micropenis	[39]
S107X	320C>A	IgI	sporadic	–	[34]
S107X	320C>A	IgI	familial		[36]
D129A	385A>C	IgI-IgII linker	sporadic	cleft palate	[33]
A167S[b]	499G>T	IgI-IgII linker	sporadic	cleft palate, corpus callosum agenesis, unilateral hearing loss, fusion of the fourth and fifth metacarpal bones	[32]
C178S[a]	535G>C	IgII	sporadic	normal sense of smell	[37]
				cryptorchidism, cleft palate, dental agenesis, external ears agenesis, right mandibular hypoplasia, hypertelorism	
D224H	670G>C	IgII	familial	cryptorchidism, micropenis	[39]
G237S[a]	709G>A	IgII	familial	normal sense of smell	[41]
G237D	710G>A	IgII	familial	–	[39]
L245P	734T>C	IgII-IgIII linker	sporadic	cleft lip and palate	[35]
R250W	748C>T	IgII-IgIII linker	familial	mental deficiency, epilepsy	[35]
R250W	748C>T	IgII-IgIII linker	sporadic	–	[35]
R254Q	761G>A	IgII-IgIII linker	sporadic	–	[39]
V273M	810G>A	IgII-IgIII linker	sporadic	cleft palate	[33]
V273M	817G>A	IgII-IgIII linker	familial	–	[39]
E274G	821G>A	IgIII	familial	cryptorchidism, micropenis	[39]
C277Y	830G>A	IgIII	sporadic	–	[32]
(donor splite)	936G>A	IgIII	familial	dental agenesis	[32]
Y339C	1016A>G	IgIII	sporadic	–	[39]
A343V	1028C>T	IgIII	familial	–	[35]
S346C	1037C>G	IgIII	familial	–	[39]
R365fsX41	1093-1094delAG	IgIII-TM linker	familial	dental agenesis	[33]
P366L	1097C>T	IgIII-TM linker	familial	obesity, sleep disorder	[35]
S439fsX461	1317_1318delTG	TM-TK linker	familial	dental agenesis	[38]
A520T	1561G>A	TK	Sporadic	–	[33]
I538V	1612A>G	TK	familial	cryptorchidism	[39]
T585X	1755C>A	TK	sporadic	–	[39]
V607M	1819G>A	TK	familial	bimanual synkinesis	[32]
Y613fsX42	1836_1837insT	TK	familial	–	[33]
K618fsX654	1852-1854delAA	TK	familial	cubitus valgus	[35]
R622G	1864C>G	TK	sporadic	cryptorchidism	[37]
				dental agenesis	
				unilateral external ear hypoplasia	
				member length asymmetry	
R622Q	1865G>A	TK	familial	cleft palate	[37]
R622X	1864C>T	TK	familial	cleft lip and palate	[32]

Table 1 continued

Mutation	Nucleotide change	Localization (domain)	Inheritance	Phenotypes	References
R622X	1864C>T	TK	familial	–	[40]
Frameshift	1970–1971delCA	TK	familial	–	[32]
W666R	1996T>A	TK	sporadic	cleft palate	[32]
(donor splite)	IVS15+1G>A	TK	sporadic	–	
Q680X[a]	2038C>T	TK	familial	normal sense of smell	[41]
(donor splite)	IVS15+1G>A	–	sporadic	–	[32]
G687R	2059G>A	TK	familial	–	[36]
G703R	2107G>C	TK	familial	cryptorchidism	[39]
G703S	2107G>A	TK	sporadic	cryptorchidism	[39]
M719R	2156T>G	TK	sporadic	–	[32]
P722S	2164C>T	TK	familial	cleft lip, bimanual synkinesis	[35]
P722H/ N724K[a]	2165C>A/ 2172C>G[c]	TK	familial	normal sense of smell cryptorchidism, dental agenesis	[41]
Y730X	2190C>G	TK	sporadic	–	[33]
P745S	2233C>T	TK	sporadic	–	[34]
P745S	2233C>T	TK	familial	micropenis	[36]
P772S	2314C>T	TK	sporadic	cleft palate, unilateral absence of nasal cartilage, iris coloboma	[32]
V795I	2383G>A	C-terminal tail	familial	–	[35]

[a] Mutations identified in normosmic patients

[b] All FGFR1 mutations were detected in heterozygous state, except the A167S mutation

[c] Mutation identified in the same allele

Ig—immunoglobulin; TM—transmembrane; TK—tyrosine kinase, C—carboxil

GnRH and GnRH receptor gene

The gene that encodes GnRH represents a natural candidate for mutations in patients with normosmic IHH. This idea was also supported by a naturally-occurring animal model of isolated HH, mice with autosomal recessive hypogonadotropic hypogonadism caused by a *GnRH* gene deletion [51]. However, no human *GnRH* deletions or mutations have thus far been identified in patients with IHH [52–55].

The human GnRH receptor gene (*GnRH-R*) has been mapped to chromosome 4q13.2–3 and spans over 18.9 Kb. It comprises three exons that encode a 328-amino acid protein [56]. The GnRH receptor belongs to the superfamily of the G protein-coupled receptor family with seven transmembrane domains and an extracellular amino terminus, but no intracellular carboxy terminus. Activation of this receptor results in increased activity of phospholipase C and mobilization of intracellular calcium [57].

Mutations in the *GnRH-R* gene were first described by de Roux et al. [58] in 1997. To date, approximately twenty different homozygous or compound heterozygous mutations have been reported in patients with sporadic or familial forms of IHH [58–64]. The two most frequent GnRH receptor mutations are Q106R and R262Q, accounting for approximately half of all reported GnRH-R mutations [65]. Both these mutations usually occur in a compound heterozygous state, and have been shown to cause partial loss of function in in vitro studies [66]. Approximately, 40% of autosomal recessive and 16% of sporadic IHH cases are due to mutations in the *GnRH-R* gene [64].

The phenotypic spectrum of normosmic IHH patients with *GnRH-R* mutations varies from partial to complete hypogonadism. Female patients with complete hypogonadism due to *GnRH-R* mutations do not respond to pulsatile GnRH treatment for infertility [67], whereas patients with partial IHH demonstrate dose-dependent responses to pulsatile GnRH in terms of gonadotropin secretion and ovulation [68]. Recently, subtle phenotypes such as apparent constitutional delay of growth and puberty and borderline oligospermia were reported in males with partial loss-of-function mutations of the GnRH receptor [69]. The mechanisms responsible for the loss of function of mutant GnRH receptors can comprise defects in the synthesis, in trafficking to the cell

membrane and/or in internalization, recycling, or degradation of receptors, in ligand binding, and/or in G-protein coupling and signal transduction.

GPR54 and *KISS1* genes

Recently, kisspeptin and its receptor GPR54 have been strongly implicated in the regulation of puberty onset. In 2003, two independent groups described inactivating mutations in the *GPR54* gene in normosmic IHH patients belonging to two consanguineous families with several affected members [70, 71]. These genetic studies established GPR54 inactivation as a new and unsuspected cause of IHH. Since then, six additional loss-of-function mutations have been described in the *GPR54* gene, comprising approximately 5% of all normosmic IHH patients investigated to date [70–73]. The majority of IHH patients identified with *GPR54* mutations are either familial or sporadic cases with consanguineous parents. In fact, considering only the familial cases of normosmic IHH, the prevalence of *GPR54* mutations increases to around 20% [70–73].

The human *GPR54* gene is located at chromosome 19p13.3 and encodes a 398-amino acid heptahelical G-protein-coupled receptor with homology to the galanin receptor family [74]. Ligand binding activates phospholipase C, increasing inositol triphosphate and resulting in the mobilization of intracellular calcium.

The endogenous ligands of the GPR54 are derived from a 145-amino acid precursor peptide, kisspeptin-1, encoded by the *KiSS1* gene. The longest of these peptides, with 54 amino acids, is kisspeptin 54 (composed by amino acids 68–121), also known as metastin. Smaller cleavage products of 14, 13 and 10 residues also occur naturally and all of them have high receptor binding affinity, which lies within the C-terminal RF-amide region [75–77]. Studies using in situ hybridization and real time PCR demonstrate that GnRH neurons co-express GPR54 transcripts. On the other hand, KiSS1 expression was demonstrated in hypothalamic areas, such as the arcuate and anteroventral periventricular nuclei, known to send projections to the medial preoptic area, where there is an abundance of GnRH cell bodies [78]. These data suggest that kisspeptin acts directly on GnRH neurons to stimulate the secretion of GnRH.

Physiological and pharmacological studies conducted in different animal models confirmed the role of the complex KiSS1/GPR54 in the reproductive axis. Mice lacking *GPR54* were also shown to have hypogonadism [71]. Interestingly, GnRH neurons were anatomically intact in these animals, with normal GnRH content, indicating that mutations in *GPR54* affect either the processing or release of this hormone and that GnRH neurons migration occurs normally [71, 79]. Additional studies demonstrated that low doses of kisspeptin, administrated either centrally or peripherally, elicit a rapid and robust secretory burst of LH and FSH in rats, mice, sheep and primates [79–85]. Moreover, this effect is blocked by the co-administration of GnRH antagonists, suggesting that kisspeptin-stimulated gonadotropin release is GnRH-release dependent and does not reflect a direct action of kisspeptin on the pituitary [80, 81, 83, 86]. Furthermore, kisspeptin administration has no effect on *GPR54–/–* mice, showing that kisspeptins act directly and uniquely through GPR54 signaling to stimulate gonadotropin release. Recently, kisspeptin was administered to humans in a double blind study. Male volunteers received kisspeptin intravenously for 90 min, resulting in significant increases in plasma concentrations of LH, FSH and testosterone as compared to saline infusion [87].

Patients carrying *GPR54* mutations present a large phenotypic spectrum, varying from partial to severe hypogonadism. Nonetheless, the majority of patients had at least partial LH and FSH responses to GnRH stimulation. The patient described by Seminara et al. [71], who had compound heterozygosity for the R331X and X399L mutations, presented at the age of 18 years with partial hypogonadism. Although he had low basal testosterone and gonadotropin levels, response to acute GnRH stimulation (100 μg i.v.) was normal and frequent gonadotropin sampling revealed the presence of low amplitude, endogenous LH pulses. On the other end of the spectrum, Semple et al. described a compound heterozygote (C223R/R297L), who was diagnosed with hypogonadism at 2 months of age with micropenis, bilateral cryptorchidism and undetectable levels of gonadotropins, suggesting a role of kisspeptins in the activation of the hypothalamic-pituitary-gonadal axis during the neonatal or late fetal life.

Segregation analysis has shown that heterozygous carriers of GPR54 loss-of-function mutations have undergone normal pubertal development. It is also noteworthy that male and female patients have been successfully treated, either with exogenous gonadotropin or long-term pulsatile GnRH infusion, achieving fertility and normal pregnancy outcomes [71, 72]. The fact that these patients responded to exogenous GnRH infusion corroborates the experimental observations that the kisspeptins/GPR54 system acts above the GnRH receptor level, most likely stimulating GnRH secretion.

Given the importance of the Kisspeptin/GPR54 complex in control of pubertal onset, the *KiSS1* gene is another obvious candidate for genetic screening in cases of IHH. Nevertheless, among 277 patients with sporadic or familial normosmic IHH, only one alteration was described [73, 88]; a homozygous 20 nucleotide insertion in the 3′ terminal end of the coding sequence was found in a boy with micropenis and bilateral cryptorchidism diagnosed with IHH at the age

of 3 months [88]. However, no functional studies regarding this unique finding have been published so far

LH and FSH beta-subunit genes

The gonadotropins are heterodimers consisting of specific beta-subunits that are noncovalently bound to a common alpha-subunit. Selective FSH deficiency due to FSH beta-subunit gene mutations causing hypogonadism and infertility is a very rare condition. To date, three distinct FSH beta-subunit gene mutations have been described in four unrelated females and two males with hypogonadism [89–96]. These homozygous or compound heterozygous mutations often affect the seatbelt region of the protein and interfere with the synthesis and stability of the heterodimer complex. Consequently, patients were found to have undetectable serum FSH and elevated serum LH levels. Recently, we identified an FSH beta-subunit gene mutation in a Brazilian female with delayed puberty, who presented with incomplete pubertal breast development and primary amenorrhea due to a homozygous Y76X mutation [97].

Only two LH beta-subunit gene mutations have been reported in humans [98, 99]. The first was described in a male with delayed puberty, low testosterone, arrested spermatogenesis, and elevated serum LH. A homozygous Q54R missense mutation in the long loop of LH beta, which impaired binding to its receptor, was identified in this patient [98]. The second mutation was described in a 30-year-old-male with delayed puberty and infertility due to a homozygous G36D missense mutation. This mutation disrupted a vital cytosine knot motif and abrogated the heterodimerization and secretion of LH. Circulating LH levels were not detectable. Treatment with hCG promoted virilization, increased testosterone levels, and enabled normal spermatogenesis [99].

Conclusions

Recent investigations into the pathogenesis of Kallmann syndrome have pointed out the importance of anosmin-1 and FGFR1 in the olfactory and GnRH neuronal systems. *GnRH-R* and *GPR54/Kiss1* genes have been implicated in IHH etiology of normosmic patients and few mutations of the beta sub-units of LH and FSH were described in patients with selective gonadotropin deficiency. Data on the prevalence, phenotype and mutation spectrum of each genetic subtype of isolated hypogonadotropic hypogonadism are essential to improve our understanding of this complex disorder, and can be useful for directing therapy and for genetic counseling. However, a genetic basis for IHH has been established in less than 20% of cases, indicating that additional genetic causes will probably be described in the future. In addition, clinical heterogeneity is remarkable in some of these genetic forms of isolated hypogonadotropic hypogonadism, suggesting that environmental factors or epigenetic phenomena and/or modifier genes may influence the phenotype.

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References

1. Palmert MR, Boepple PA (2001) Variation in the timing of puberty: clinical spectrum and genetic investigation. J Clin Endocrinol Metab 86:2364–2368
2. Seminara SB, Hayes FJ, Crowley WF Jr (1998) Gonadotropin-releasing hormone deficiency in the human (idiopathic hypogonadotropic hypogonadism and Kallmann's syndrome): pathophysiological and genetic considerations. Endocr Rev 19:521–539
3. Pawlowitzki IH, Diekstall P, Schadel A, Miny P (1987) Estimating frequency of Kallmann syndrome among hypogonadic and among anosmic patients. Am J Med Genet 26:473–479
4. Oliveira LM, Seminara SB, Beranova M, Hayes FJ, Valkenburgh SB, Schipani E, Costa EM, Latronico AC, Crowley WF Jr, Vallejo M (2001) The importance of autosomal genes in Kallmann syndrome: genotype–phenotype correlations and neuroendocrine characteristics. J Clin Endocrinol Metab 86:1532–1538
5. Georgopoulos N, Pralong F, Seidman C, Seidman J, Crowley WJ, Vallejo M (1997) Genetic heterogeneity evidenced by low incidence of KAL-1 gene mutations in sporadic cases of gonadotropin-releasing hormone deficiency. J Clin Endocrinol Metab 82:213–217
6. Waldstreicher J, Seminara SB, Jameson JL, Geyer A, Nachtigall LB, Boepple PA, Holmes LB, Crowley WF Jr (1996) The genetic and clinical heterogeneity of gonadotropin-releasing hormone deficiency in the human. J Clin Endocrinol Metab 81:4388–4395
7. Schwanzel-Fukuda M, Pfaff DW (1989) Origin of luteinizing hormone-releasing hormone neurons. Nature 338:161–164
8. Wray S, Grant P, Gainer H (1989) Evidence that cells expressing luteinizing hormone-releasing hormone mRNA in the mouse are derived from progenitor cells in the olfactory placode. Proc Natl Acad Sci USA 86:8132–8136
9. Tobet SA, Bless EP, Schwarting GA (2001) Developmental aspect of the gonadotropin-releasing hormone system. Mol Cell Endocrinol 185:173–184
10. Franco B, Guioli S, Pragliola A, Incerti B, Bardoni B, Tonlorenzi R, Carrozzo R, Maestrini E, Pieretti M, Taillon-Miller P et al (1991) A gene deleted in Kallmann's syndrome shares homology with neural cell adhesion and axonal path-finding molecules. Nature 353:529–536
11. Legouis R, Hardelin JP, Levilliers J, Claverie JM, Compain S, Wunderle V, Millasseau P, Le Paslier D, Cohen D, Caterina D et al (1991) The candidate gene for the X-linked Kallmann syndrome encodes a protein related to adhesion molecules. Cell 67:423–435
12. Hardelin JP, Julliard AK, Moniot B, Soussi-Yanicostas N, Verney C, Schwanzel-Fukuda M, Ayer-Le Lievre C, Petit C (1999) Anosmin-1 is a regionally restricted component of basement membranes and interstitial matrices during organogenesis: implications for the developmental anomalies of X chromosome-linked Kallmann syndrome. Dev Dyn 215:26–44

13. Schwanzel-Fukuda M, Bick D, Pfaff DW (1989) Luteinizing hormone-releasing hormone (LHRH)-expressing cells do not migrate normally in an inherited hypogonadal (Kallmann) syndrome. Brain Res Mol Brain Res 6:311–326
14. Madan R, Sawlani V, Gupta S, Phadke RV (2004) MRI findings in Kallmann syndrome. Neurol India 52:501–503
15. Massin N, Pecheux C, Eloit C, Bensimon JL, Galey J, Kuttenn F, Hardelin JP, Dode C, Touraine P (2003) X chromosome-linked Kallmann syndrome: clinical heterogeneity in three siblings carrying an intragenic deletion of the KAL-1 gene. J Clin Endocrinol Metab 88:2003–2008
16. Tsai PS, Gill JC (2006) Mechanisms of disease: Insights into X-linked and autosomal-dominant Kallmann syndrome. Nat Clin Pract Endocrinol Metab 2:160–171
17. Pitteloud N, Hayes FJ, Boepple PA, DeCruz S, Seminara SB, MacLaughlin DT, Crowley WF Jr (2002) 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 87:152–160
18. White BJ, Rogol AD, Brown KS, Lieblich JM, Rosen SW (1983) The syndrome of anosmia with hypogonadotropic hypogonadism: a genetic study of 18 new families and a review. Am J Med Genet 15:417–435
19. Zenteno JC, Mendez JP, Maya-Nunez G, Ulloa-Aguirre A, Kofman-Alfaro S (1999) Renal abnormalities in patients with Kallmann syndrome. BJU Int 83:383–386
20. Schwankhaus JD, Currie J, Jaffe MJ, Rose SR, Sherins RJ (1989) Neurologic findings in men with isolated hypogonadotropic hypogonadism. Neurology 39:223–226
21. Mayston MJ, Harrison LM, Quinton R, Stephens JA, Krams M, Bouloux PM (1997) Mirror movements in X-linked Kallmann's syndrome. I. A neurophysiological study. Brain 120(Pt 7):1199–1216
22. Dode C, Hardelin JP (2004) Kallmann syndrome: fibroblast growth factor signaling insufficiency? J Mol Med 82:725–734
23. Quinton R, Duke VM, de Zoysa PA, Platts AD, Valentine A, Kendall B, Pickman S, Kirk JM, Besser GM, Jacobs HS, Bouloux PM (1996) The neuroradiology of Kallmann's syndrome: a genotypic and phenotypic analysis. J Clin Endocrinol Metab 81:3010–3017
24. Cariboni A, Pimpinelli F, Colamarino S, Zaninetti R, Piccolella M, Rumio C, Piva F, Rugarli EI,Maggi R (2004) The product of X-linked Kallmann's syndrome gene (KAL1) affects the migratory activity of gonadotropin-releasing hormone (GnRH)-producing neurons. Hum Mol Genet 13:2781–2791
25. Rugarli EI, Di Schiavi E, Hilliard MA, Arbucci S, Ghezzi C, Facciolli A, Coppola G, Ballabio A, Bazzicalupo P (2002) The Kallmann syndrome gene homolog in C. elegans is involved in epidermal morphogenesis and neurite branching. Development 129:1283–1294
26. Soussi-Yanicostas N, de Castro F, Julliard AK, Perfettini I, Chedotal A,Petit C (2002) Anosmin-1, defective in the X-linked form of Kallmann syndrome, promotes axonal branch formation from olfactory bulb output neurons. Cell 109:217–228
27. Soussi-Yanicostas N, Faivre-Sarrailh C, Hardelin JP, Levilliers J, Rougon G,Petit C (1998) Anosmin-1 underlying the X chromosome-linked Kallmann syndrome is an adhesion molecule that can modulate neurite growth in a cell-type specific manner. J Cell Sci 111(Pt 19):2953–2965
28. Hu Y, Sun Z, Eaton JT, Bouloux PM,Perkins SJ (2005) Extended and flexible domain solution structure of the extracellular matrix protein anosmin-1 by X-ray scattering, analytical ultracentrifugation and constrained modelling. J Mol Biol 350:553–570
29. Hu Y, Gonzalez-Martinez D, Kim SH, Bouloux PM (2004) Cross-talk of anosmin-1, the protein implicated in X-linked Kallmann's syndrome, with heparan sulphate and urokinase-type plasminogen activator. Biochem J 384:495–505
30. Bulow HE, Berry KL, Topper LH, Peles E, Hobert O (2002) Heparan sulfate proteoglycan-dependent induction of axon branching and axon misrouting by the Kallmann syndrome gene kal-1. Proc Natl Acad Sci USA 99:6346–6351
31. Andrenacci D, Grimaldi MR, Panetta V, Riano E, Rugarli EI, Graziani F (2006) Functional dissection of the Drosophila Kallmann's syndrome protein DmKal-1. BMC Genet 7:47
32. 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 (2003) Loss-of-function mutations in FGFR1 cause autosomal dominant Kallmann syndrome. Nat Genet 33:463–465
33. Albuisson J, Pecheux C, Carel JC, Lacombe D, Leheup B, Lapuzina P, Bouchard P, Legius E, Matthijs G, Wasniewska M, Delpech M, Young J, Hardelin JP, Dode C (2005) Kallmann syndrome: 14 novel mutations in KAL1 and FGFR1 (KAL2). Hum Mutat 25:98–99
34. 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 (2004) 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 89:1079–1088
35. Trarbach EB, Costa EM, Versiani B, de Castro M, Baptista MT, Garmes HM, de Mendonca BB, Latronico AC (2006) Novel fibroblast growth factor receptor 1 mutations in patients with congenital hypogonadotropic hypogonadism with and without anosmia. J Clin Endocrinol Metab 91:4006–4012
36. Sato N, Hasegawa T, Hori N, Fukami M, Yoshimura Y, Ogata T (2005) Gonadotrophin therapy in Kallmann syndrome caused by heterozygous mutations of the gene for fibroblast growth factor receptor 1: report of three families: case report. Hum Reprod 20:2173–2178
37. Zenaty D, Bretones P, Lambe C, Guemas I, David M, Leger J, de Roux N (2006) Paediatric phenotype of Kallmann syndrome due to mutations of fibroblast growth factor receptor 1 (FGFR1). Mol Cell Endocrinol 254–255:78–83
38. Sato N, Ohyama K, Fukami M, Okada M, Ogata T (2006) Kallmann syndrome: somatic and germline mutations of the fibroblast growth factor receptor 1 gene in a mother and the son. J Clin Endocrinol Metab 91:1415–1418
39. 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 (2006) Mutations in fibroblast growth factor receptor 1 cause Kallmann syndrome with a wide spectrum of reproductive phenotypes. Mol Cell Endocrinol 254–255:60–69
40. Pitteloud N, Acierno JS Jr, Meysing AU, Dwyer AA, Hayes FJ, Crowley WF Jr (2005) Reversible kallmann syndrome, delayed puberty, and isolated anosmia occurring in a single family with a mutation in the fibroblast growth factor receptor 1 gene. J Clin Endocrinol Metab 90:1317–1322
41. 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 (2006) Mutations in fibroblast growth factor receptor 1 cause both Kallmann syndrome and normosmic idiopathic hypogonadotropic hypogonadism. Proc Natl Acad Sci USA 103:6281–6286

42. Kim HG, Herrick SR, Lemyre E, Kishikawa S, Salisz JA, Seminara S, MacDonald ME, Bruns GA, Morton CC, Quade BJ, Gusella JF (2005) Hypogonadotropic hypogonadism and cleft lip and palate caused by a balanced translocation producing haploinsufficiency for FGFR1. J Med Genet 42:666–672
43. Groth C,Lardelli M (2002) The structure and function of vertebrate fibroblast growth factor receptor 1. Int J Dev Biol 46:393–400
44. McKeehan WL, Kan M (1994) Heparan sulfate fibroblast growth factor receptor complex: structure-function relationships. Mol Reprod Dev 39:69–81; discusison 81–62
45. Ibrahimi OA, Zhang F, Hrstka SC, Mohammadi M, Linhardt RJ (2004) Kinetic model for FGF, FGFR, and proteoglycan signal transduction complex assembly. Biochemistry 43:4724–4730
46. Gonzalez-Martinez D, Kim SH, Hu Y, Guimond S, Schofield J, Winyard P, Vannelli GB, Turnbull J, Bouloux PM (2004) Anosmin-1 modulates fibroblast growth factor receptor 1 signaling in human gonadotropin-releasing hormone olfactory neuroblasts through a heparan sulfate-dependent mechanism. J Neurosci 24:10384–10392
47. Hebert JM, Lin M, Partanen J, Rossant J, McConnell SK (2003) FGF signaling through FGFR1 is required for olfactory bulb morphogenesis. Development 130:1101–1111
48. Bribian A, Barallobre MJ, Soussi-Yanicostas N, de Castro F (2006) Anosmin-1 modulates the FGF-2-dependent migration of oligodendrocyte precursors in the developing optic nerve. Mol Cell Neurosci 33:2–14
49. 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 (2006) Abnormal development of the olfactory bulb and reproductive system in mice lacking prokineticin receptor PKR2. Proc Natl Acad Sci USA 103:4140–4145
50. Dode C, Teixeira L, Levilliers J, Fouveaut C, Bouchard P, Kottler ML, Lespinasse J, Lienhardt-Roussie A, Mathieu M, Moerman A, Morgan G, Murat A, Toublanc JE, Wolczynski S, Delpech M, Petit C, Young J, Hardelin JP (2006) Kallmann syndrome: mutations in the genes encoding prokineticin-2 and prokineticin receptor-2. PLoS Genet 2:e175
51. Mason AJ, Hayflick JS, Zoeller RT, Young WS 3rd, Phillips HS, Nikolics K, Seeburg PH (1986) A deletion truncating the gonadotropin-releasing hormone gene is responsible for hypogonadism in the hpg mouse. Science 234:1366–1371
52. Vagenakis GA, Sgourou A, Papachatzopoulou A, Kourounis G, Papavassiliou AG, Georgopoulos NA (2005) The gonadotropin-releasing hormone (GnRH)-1 gene, the GnRH receptor gene, and their promoters in patients with idiopathic hypogonadotropic hypogonadism with or without resistance to GnRH action. Fertil Steril 84:1762–1765
53. Bo-Abbas Y, Acierno JS Jr, Shagoury JK, Crowley WF Jr, Seminara SB (2003) Autosomal recessive idiopathic hypogonadotropic hypogonadism: genetic analysis excludes mutations in the gonadotropin-releasing hormone (GnRH) and GnRH receptor genes. J Clin Endocrinol Metab 88:2730–2737
54. Layman LC, Wilson JT, Huey LO, Lanclos KD, Plouffe L Jr, McDonough PG (1992) Gonadotropin-releasing hormone, follicle-stimulating hormone beta, luteinizing hormone beta gene structure in idiopathic hypogonadotropic hypogonadism. Fertil Steril 57:42–49
55. Weiss J, Adams E, Whitcomb RW, Crowley WF Jr, Jameson JL (1991) Normal sequence of the gonadotropin-releasing hormone gene in patients with idiopathic hypogonadotropic hypogonadism. Biol Reprod 45:743–747
56. Kaiser UB, Dushkin H, Altherr MR, Beier DR, Chin WW (1994) Chromosomal localization of the gonadotropin-releasing hormone receptor gene to human chromosome 4q13.1-q21.1 and mouse chromosome 5. Genomics 20:506–508
57. Kakar SS, Musgrove LC, Devor DC, Sellers JC, Neill JD (1992) Cloning, sequencing, and expression of human gonadotropin releasing hormone (GnRH) receptor. Biochem Biophys Res Commun 189:289–295
58. de Roux N, Young J, Misrahi M, Genet R, Chanson P, Schaison G, Milgrom E (1997) A family with hypogonadotropic hypogonadism and mutations in the gonadotropin-releasing hormone receptor. N Engl J Med 337:1597–1602
59. Layman LC, Cohen DP, Jin M, Xie J, Li Z, Reindollar RH, Bolbolan S, Bick DP, Sherins RR, Duck LW, Musgrove LC, Sellers JC, Neill JD (1998) Mutations in gonadotropin-releasing hormone receptor gene cause hypogonadotropic hypogonadism. Nat Genet 18:14–15
60. Costa EM, Bedecarrats GY, Mendonca BB, Arnhold IJ, Kaiser UB, Latronico AC (2001) Two novel mutations in the gonadotropin-releasing hormone receptor gene in Brazilian patients with hypogonadotropic hypogonadism and normal olfaction. J Clin Endocrinol Metab 86:2680–2686
61. de Roux N, Young J, Brailly-Tabard S, Misrahi M, Milgrom E,Schaison G (1999) The same molecular defects of the gonadotropin-releasing hormone receptor determine a variable degree of hypogonadism in affected kindred. J Clin Endocrinol Metab 84:567–572
62. Caron P, Chauvin S, Christin-Maitre S, Bennet A, Lahlou N, Counis R, Bouchard P, Kottler ML (1999) Resistance of hypogonadic patients with mutated GnRH receptor genes to pulsatile GnRH administration. J Clin Endocrinol Metab 84:990–996
63. Seminara SB, Beranova M, Oliveira LM, Martin KA, Crowley WF Jr, Hall JE (2000) Successful use of pulsatile gonadotropin-releasing hormone (GnRH) for ovulation induction and pregnancy in a patient with GnRH receptor mutations. J Clin Endocrinol Metab 85:556–562
64. Beranova M, Oliveira LM, Bedecarrats GY, Schipani E, Vallejo M, Ammini AC, Quintos JB, Hall JE, Martin KA, Hayes FJ, Pitteloud N, Kaiser UB, Crowley WF Jr, Seminara SB (2001) Prevalence, phenotypic spectrum, and modes of inheritance of gonadotropin-releasing hormone receptor mutations in idiopathic hypogonadotropic hypogonadism. J Clin Endocrinol Metab 86:1580–1588
65. Bhagavath B, Podolsky RH, Ozata M, Bolu E, Bick DP, Kulharya A, Sherins RJ, Layman LC (2006) Clinical and molecular characterization of a large sample of patients with hypogonadotropic hypogonadism. Fertil Steril 85:706–713
66. Bedecarrats GY, Linher KD, Kaiser UB (2003) Two common naturally occurring mutations in the human gonadotropin-releasing hormone (GnRH) receptor have differential effects on gonadotropin gene expression and on GnRH-mediated signal transduction. J Clin Endocrinol Metab 88:834–843
67. Meysing AU, Kanasaki H, Bedecarrats GY, Acierno JS Jr, Conn PM, Martin KA, Seminara SB, Hall JE, Crowley WF Jr, Kaiser UB (2004) GNRHR mutations in a woman with idiopathic hypogonadotropic hypogonadism highlight the differential sensitivity of luteinizing hormone and follicle-stimulating hormone to gonadotropin-releasing hormone. J Clin Endocrinol Metab 89:3189–3198
68. Kottler ML, Counis R,Bouchard P (1999) Mutations of the GnRH receptor gene: a new cause of autosomal-recessive hypogonadotropic hypogonadism. Arch Med Res 30:481–485
69. Lin L, Conway GS, Hill NR, Dattani MT, Hindmarsh PC, Achermann JC (2006) A homozygous R262Q mutation in the gonadotropin-releasing hormone receptor (GNRHR) presenting as constitutional delay of growth and puberty with subsequent borderline oligospermia. J Clin Endocrinol Metab

70. de Roux N, Genin E, Carel JC, Matsuda F, Chaussain JL, Milgrom E (2003) Hypogonadotropic hypogonadism due to loss of function of the KiSS1-derived peptide receptor GPR54. Proc Natl Acad Sci USA 100:10972–10976
71. Seminara SB, Messager S, Chatzidaki EE, Thresher RR, Acierno JS Jr, Shagoury JK, Bo-Abbas Y, Kuohung W, Schwinof KM, Hendrick AG, Zahn D, Dixon J, Kaiser UB, Slaugenhaupt SA, Gusella JF, O'Rahilly S, Carlton MB, Crowley WF Jr, Aparicio SA,Colledge WH (2003) The GPR54 gene as a regulator of puberty. N Engl J Med 349:1614–1627
72. Lanfranco F, Gromoll J, von Eckardstein S, Herding EM, Nieschlag E,Simoni M (2005) Role of sequence variations of the GnRH receptor and G protein-coupled receptor 54 gene in male idiopathic hypogonadotropic hypogonadism. Eur J Endocrinol 153:845–852
73. Semple RK, Achermann JC, Ellery J, Farooqi IS, Karet FE, Stanhope RG, O'Rahilly S, Aparicio SA (2005) Two novel missense mutations in g protein-coupled receptor 54 in a patient with hypogonadotropic hypogonadism. J Clin Endocrinol Metab 90:1849–1855
74. Lee DK, Nguyen T, O'Neill GP, Cheng R, Liu Y, Howard AD, Coulombe N, Tan CP, Tang-Nguyen AT, George SR, O'Dowd BF (1999) Discovery of a receptor related to the galanin receptors. FEBS Lett 446:103–107
75. Kotani M, Detheux M, Vandenbogaerde A, Communi D, Vanderwinden JM, Le Poul E, Brezillon S, Tyldesley R, Suarez-Huerta N, Vandeput F, Blanpain C, Schiffmann SN, Vassart G,Parmentier M (2001) The metastasis suppressor gene KiSS-1 encodes kisspeptins, the natural ligands of the orphan G protein-coupled receptor GPR54. J Biol Chem 276:34631–34636
76. Muir AI, Chamberlain L, Elshourbagy NA, Michalovich D, Moore DJ, Calamari A, Szekeres PG, Sarau HM, Chambers JK, Murdock P, Steplewski K, Shabon U, Miller JE, Middleton SE, Darker JG, Larminie CG, Wilson S, Bergsma DJ, Emson P, Faull R, Philpott KL, Harrison DC (2001) AXOR12, a novel human G protein-coupled receptor, activated by the peptide KiSS-1. J Biol Chem 276:28969–28975
77. Ohtaki T, Shintani Y, Honda S, Matsumoto H, Hori A, Kanehashi K, Terao Y, Kumano S, Takatsu Y, Masuda Y, Ishibashi Y, Watanabe T, Asada M, Yamada T, Suenaga M, Kitada C, Usuki S, Kurokawa T, Onda H, Nishimura O, Fujino M (2001) Metastasis suppressor gene KiSS-1 encodes peptide ligand of a G-protein-coupled receptor. Nature 411:613–617
78. Smith JT, Clifton DK,Steiner RA (2006) Regulation of the neuroendocrine reproductive axis by kisspeptin-GPR54 signaling. Reproduction 131:623–630
79. Messager S, Chatzidaki EE, Ma D, Hendrick AG, Zahn D, Dixon J, Thresher RR, Malinge I, Lomet D, Carlton MB, Colledge WH, Caraty A, Aparicio SA (2005) Kisspeptin directly stimulates gonadotropin-releasing hormone release via G protein-coupled receptor 54. Proc Natl Acad Sci USA 102:1761–1766
80. Gottsch ML, Cunningham MJ, Smith JT, Popa SM, Acohido BV, Crowley WF, Seminara S, Clifton DK, Steiner RA (2004) A role for kisspeptins in the regulation of gonadotropin secretion in the mouse. Endocrinology 145:4073–4077
81. Irwig MS, Fraley GS, Smith JT, Acohido BV, Popa SM, Cunningham MJ, Gottsch ML, Clifton DK, Steiner RA (2004) Kisspeptin activation of gonadotropin releasing hormone neurons and regulation of KiSS-1 mRNA in the male rat. Neuroendocrinology 80:264–272
82. Matsui H, Takatsu Y, Kumano S, Matsumoto H, Ohtaki T (2004) Peripheral administration of metastin induces marked gonadotropin release and ovulation in the rat. Biochem Biophys Res Commun 320:383–388
83. Shahab M, Mastronardi C, Seminara SB, Crowley WF, Ojeda SR, Plant TM (2005) Increased hypothalamic GPR54 signaling: a potential mechanism for initiation of puberty in primates. Proc Natl Acad Sci USA 102:2129–2134
84. Plant TM, Ramaswamy S, Dipietro MJ (2006) Repetitive activation of hypothalamic G protein-coupled receptor 54 with intravenous pulses of kisspeptin in the juvenile monkey (Macaca mulatta) elicits a sustained train of gonadotropin-releasing hormone discharges. Endocrinology 147:1007–1013
85. Navarro VM, Castellano JM, Fernandez-Fernandez R, Barreiro ML, Roa J, Sanchez-Criado JE, Aguilar E, Dieguez C, Pinilla L, Tena-Sempere M (2004) Developmental and hormonally regulated messenger ribonucleic acid expression of KiSS-1 and its putative receptor, GPR54, in rat hypothalamus and potent luteinizing hormone-releasing activity of KiSS-1 peptide. Endocrinology 145:4565–4574
86. Navarro VM, Castellano JM, Fernandez-Fernandez R, Tovar S, Roa J, Mayen A, Nogueiras R, Vazquez MJ, Barreiro ML, Magni P, Aguilar E, Dieguez C, Pinilla L, Tena-Sempere M (2005) Characterization of the potent luteinizing hormone-releasing activity of KiSS-1 peptide, the natural ligand of GPR54. Endocrinology 146:156–163
87. Dhillo WS, Chaudhri OB, Patterson M, Thompson EL, Murphy KG, Badman MK, McGowan BM, Amber V, Patel S, Ghatei MA, Bloom SR (2005) Kisspeptin-54 stimulates the hypothalamic-pituitary gonadal axis in human males. J Clin Endocrinol Metab 90:6609–6615
88. De Roux N, Acierno J, Houang M, Derbois D, Matsuda F, Meysing A, Pugeat M, Le Bouc Y, Crowley WJ, Kelly P,Seminara S (2004) An unique short 3′ duplication of the coding sequence of the GPR54 ligand identified in a large cohort of isolated hypogonadotropic hypogonadism patients. Endocrine society's 86th annual meeting
89. Matthews CH, Borgato S, Beck-Peccoz P, Adams M, Tone Y, Gambino G, Casagrande S, Tedeschini G, Benedetti A, Chatterjee VK (1993) Primary amenorrhoea and infertility due to a mutation in the beta-subunit of follicle-stimulating hormone. Nat Genet 5:83–86
90. Layman LC, Lee EJ, Peak DB, Namnoum AB, Vu KV, van Lingen BL, Gray MR, McDonough PG, Reindollar RH,Jameson JL (1997) Delayed puberty and hypogonadism caused by mutations in the follicle-stimulating hormone beta-subunit gene. N Engl J Med 337:607–611
91. Matthews C,Chatterjee VK (1997) Isolated deficiency of follicle-stimulating hormone re-revisited. N Engl J Med 337:642
92. Rabin D, Spitz I, Bercovici B, Bell J, Laufer A, Benveniste R,Polishuk W (1972) Isolated deficiency of follicle-stimulating hormone. Clinical and laboratory features. N Engl J Med 287:1313–1317
93. Rabinowitz D, Benveniste R, Linder J, Lorber D,Daniell J (1979) Isolated follicle-stimulating hormone deficiency revisited. Ovulation and conception in presence of circulating antibody to follicle-stimulating hormone. N Engl J Med 300:126–128
94. Layman LC, Porto AL, Xie J, da Motta LA, da Motta LD, Weiser W,Sluss PM (2002) FSH beta gene mutations in a female with partial breast development and a male sibling with normal puberty and azoospermia. J Clin Endocrinol Metab 87:3702–3707
95. Lindstedt G, Nystrom E, Matthews C, Ernest I, Janson PO,Chatterjee K (1998) Follitropin (FSH) deficiency in an infertile male due to FSHbeta gene mutation. A syndrome of normal puberty and virilization but underdeveloped testicles with azoospermia, low FSH but high lutropin and normal serum testosterone concentrations. Clin Chem Lab Med 36:663–665
96. Phillip M, Arbelle JE, Segev Y,Parvari R (1998) Male hypogonadism due to a mutation in the gene for the beta-subunit of follicle-stimulating hormone. N Engl J Med 338:1729–1732

97. Berger K, Souza H, Brito VN, d'Alva CB, Mendonca BB,Latronico AC (2005) Clinical and hormonal features of selective follicle-stimulating hormone (FSH) deficiency due to FSH beta-subunit gene mutations in both sexes. Fertil Steril 83:466–470
98. Weiss J, Axelrod L, Whitcomb RW, Harris PE, Crowley WF,Jameson JL (1992) Hypogonadism caused by a single amino acid substitution in the beta subunit of luteinizing hormone. N Engl J Med 326:179–183
99. Valdes-Socin H, Salvi R, Daly AF, Gaillard RC, Quatresooz P, Tebeu PM, Pralong FP,Beckers A (2004) Hypogonadism in a patient with a mutation in the luteinizing hormone beta-subunit gene. N Engl J Med 351:2619–2625