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The genetic and molecular basis of idiopathic hypogonadotropic hypogonadism

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Abstract

Idiopathic hypogonadotropic hypogonadism (IHH) has an incidence of 1–10 cases per 100,000 births. About 60% of patients with IHH present with associated anosmia, also known as Kallmann syndrome, characterized by total or partial loss of olfaction. Many of the gene mutations associated with Kallmann syndrome have been mapped to *KAL1* or *FGFR1*. However, together, these mutations account for only about 15% of Kallmann syndrome cases. More recently, mutations in *PROK2* and *PROKR2* have been linked to the syndrome and may account for an additional 5–10% of cases. The remaining 40% of patients with IHH have a normal sense of smell. Prior to 2003, the only gene linked to normosmic IHH was the gonadotropin-releasing hormone receptor gene. However, mutations in this receptor are believed to account for only 10% of cases. Subsequently, mutations in *KISS1R*, *TAC3* and *TACR3* were identified as causes of normosmic IHH. Certain genes, including *PROK2* and *FGFR1*, are associated with both anosmic and normosmic IHH. Despite recent advances in the field, the genetic causes of the majority of cases of IHH remain unknown. This Review discusses genes associated with hypogonadotropic disorders and the molecular mechanisms by which mutations in these genes may result in IHH.

Introduction

Idiopathic hypogonadotropic hypogonadism (IHH) is characterized by delayed or absent sexual development associated with inappropriately low gonadotropin and sex steroid levels in the absence of anatomical or functional abnormalities of the hypothalamic–pituitary–gonadal axis. The major underlying cause of IHH is failure to activate pulsatile secretion of gonadotropin-releasing hormone (GnRH) during puberty, a developmental stage characterized by a substantial increase in the frequency and amplitude of pulses of this hormone.

To date, the greatest insights into the molecular mechanisms that regulate activation of GnRH have been provided by the identification and study of genetic abnormalities in patients with pubertal disorders or infertility.[1] Other abnormal phenotypes that are commonly associated with and segregate with hypogonadism in affected families have also helped to identify the underlying molecular defects. The most common associated phenotype is anosmia, an inability to perceive smells, which is explained by the common embryonic origins and developmental

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pathways of GnRH and olfactory neurons. The development of GnRH neurons is unusual in that they originate outside the brain. Similar to the development of olfactory fibers, GnRH neurons are formed in the nasal placode (olfactory epithelium), from which they migrate by use of the olfactory pathway to help guide them to their ultimate destination in the hypothalamus.[2]

Impaired migration of GnRH and olfactory neurons is the underlying cause of Kallmann syndrome (IHH associated with anosmia). Accordingly, gene mutations associated with Kallmann syndrome encode proteins that regulate GnRH and olfactory neuronal migration. Other associated neurological and somatic abnormalities, such as synkinesia, cerebellar ataxia, sensorineural deafness, mental retardation, unilateral renal agenesis and cleft palate, may segregate with the Kallmann syndrome phenotype, which suggests a common genetic origin of these abnormalities.[3] The genetic mechanisms that underlie IHH in patients with a normal sense of smell are diverse and may involve genes that regulate development and/or GnRH secretion or action.

In some cases, the severity of hypogonadism and the presence of associated phenotypes in a pedigree present in a dimorphic distribution with incomplete penetrance. This pattern suggests that changes may occur in more than one gene and/or that sex-associated modifying factors may contribute to the phenotype.[4–6] Evidence for the contribution of sex-associated factors in IHH is reinforced by the 5:1 male predominance of the disorder. In addition, male patients often present with a more severe phenotype than affected female individuals within a given family.

In this Review, we will discuss genes associated with IHH. The genes have been categorized according to whether the proteins they encode are involved in the development and migration of GnRH neurons, regulation of GnRH secretion or GnRH action (Table 1, Figure 1). We have focused primarily on genes that encode ligand–receptor pairs. Functional characterization of these mutations has shed light on the pathophysiology of IHH. Additional genes implicated in IHH include *NELF* (nasal embryonic LHRH factor) and genes that encode a host of transcription factors, most notably nuclear receptor DAX-1 and steroidogenic factor 1, but discussion of these is beyond the scope of this Review.

Migration of GnRH neurons

KAL1

KAL1 is located on the X chromosome and encodes an extracellular cell adhesion protein, anosmin 1, essential for axonal guidance and migration of olfactory and GnRH neurons from the nasal placode to their final location in the brain.[7] Anosmin 1 co-localizes with basic fibroblast growth factor receptor 1 (FGFR-1, discussed further below), in the olfactory bulb during development, which suggests that this protein is a component of FGFR-1 signaling.[8] Mutations in *KAL1* disrupt the migration of olfactory and GnRH neurons and are reported to be present in approximately 5–10% of patients with Kallmann syndrome (Table 1),[7,9–11] with the highest prevalence seen in families with X-linked inheritance patterns.

The *KAL1* gene comprises 14 exons and encodes a 680 amino acid protein with a complex structure that includes an N-terminal signal peptide followed by a cysteine-rich region, a whey acidic protein-like domain, four tandem repeats of fibronectin-like type III domains, and a C-terminal histidine-rich region.[12] The *KAL1* mutations identified to date predominantly consist of nucleotide deletions or insertions that result in sequence frameshifts or the introduction of premature stop codons. Less than 20% of the different mutations associated with Kallmann syndrome result in amino acid substitutions.[13] Two amino acid changes in the whey acidic protein-like domain have been described: Cys163Tyr and Cys172Arg. This domain contains

two conserved disulfide bond motifs (Cys151–Cys163 and Cys157–Cys172). The Cys163Tyr and Cys172Arg mutations are expected to prevent disulfide bond formation, which disrupts the tertiary structure of anosmin 1 and might result in misfolding and/or destabilization of the protein.

All the other amino acid substitutions in anosmin 1 that are associated with Kallmann syndrome are located in the fibronectin-like type III domains. All four of these domains have N-glycosylation sites as well as potential heparin binding sites. Two mutations (Asn267Lys and Glu514Lys) are expected to enhance heparin binding, which compromises the flexibility of anosmin 1.[13] Reversal of hypogonadism has been described in a patient with a frameshift mutation in *KAL1* that introduced a premature stop codon at amino acid 85. If expressed, this mutant anosmin 1 encodes a truncated protein that lacks 525 of its 610 amino acids. Reversibility of the phenotype in this case raises the possibility that this truncated mutant may somehow retain some biological activity, or that other pathways may compensate for the lack of activity of the defective anosmin 1.[14]

FGFR1

The protein encoded by *FGFR1*—FGFR-1—is a member of the tyrosine kinase superfamily of receptors. FGFR-1 contains an extracellular domain that has three immunoglobulin-like domains (D1, D2 and D3); these domains dictate the receptor's affinity and specificity for its ligands. The protein also includes a single transmembrane helix and an intracellular domain with tyrosine kinase activity. In the presence of heparin sulfate, fibroblast growth factor binds FGFR-1 with high affinity, stimulating receptor dimerization and trans-autophosphorylation of tyrosine residues in the intracellular domain. These steps result in activation of downstream signaling. The major signaling pathway activated is the mitogen-activated protein kinase pathway. FGFR-1 signaling through this pathway regulates neuronal migration, differentiation, and survival, as well as cell proliferation during embryonic development.[15–17]

Kallmann syndrome caused by mutations in *FGFR1* is typically transmitted in an autosomal dominant fashion and can be associated with failed morphogenesis of the olfactory bulbs, cleft palate and dental agenesis. The severity of the hypogonadism and the presence of associated phenotypes have variable expressivity with incomplete penetrance.[18] Mutations in *FGFR1* account for approximately 10% of Kallmann cases (Table 1). Unlike the situation with *KAL1* mutations, mutations in *FGFR1* have been reported in patients with IHH without anosmia, termed normosmic IHH.

The majority of *FGFR1* mutations associated with Kallmann syndrome are single amino acid substitutions located in the immunoglobulin-like domains or tyrosine kinase domain. A Gly237Asp substitution in the second immunoglobulin-like domain removes a highly conserved glycine that is predicted to maintain structural integrity of the protein. *In vitro* studies indicate that a serine substitution at this position destabilizes the receptor, which results in misfolding and retention of the protein in the endoplasmic reticulum.[4] An Asp224His substitution, also in the second immunoglobulin-like domain, is believed to prevent ligand-induced or heparin-sulfate-induced FGFR-1 dimerization and signaling.[5] Amino acid substitutions that map to the third immunoglobulin-like domain of FGFR-1, such as Val273Met, Glu274Gly, Tyr339Cys, and Ser346Cys, are predicted to disrupt a characteristic Cys277–Cys341 disulfide bond in this domain.[4,5] Mutations in the tyrosine kinase domain of FGFR-1 are predicted to decrease or inhibit kinase activity by disrupting receptor conformation (Ile538Val, Asn724Lys, and Gly703Arg) and/or altering the normal pattern of phosphorylation of the kinase domain (Ala520Thr, Gly703Ser, Pro722Ser, Pro745Ser, and Pro772Ser).[5,13,17]

Reversal of IHH after testosterone treatment has been reported in a patient harboring a heterozygous mutation in the tyrosine kinase domain of FGFR-1 (Arg622X). The creation of

the stop codon in the tyrosine kinase domain by this mutation results in a truncated protein.[19] Two family members carrying the same mutation were reported to have delayed puberty (mother) and anosmia (maternal grandfather). Reversal of IHH in this case suggests that FGFR-1 might regulate reproduction beyond the stage of embryonic GnRH neuronal migration.[19] The reversal also raises the possibility that hormone replacement with testosterone may provide the assistance needed for compensation for GnRH deficiency in such cases.

Mutations in the gene *FGF8*, which encodes one of the many ligands of FGFR-1, have recently been linked to Kallmann syndrome. This finding suggests that FGF-8 is the FGFR-1 ligand responsible for GnRH neuronal development and/or migration.[20]

PROK2 and PROKR2

PROKR2 encodes a G-protein-coupled receptor, prokineticin receptor 2 (PK-R2), and *PROK2* encodes one of its ligands, prokineticin-2 (PK2). When PK2 binds to PK-R2, signaling cascades that are important for development of the olfactory system and GnRH neuronal progenitors are initiated.[21–24] Mutations in PK2 or PK-R2 are estimated to account for 5–10% of all Kallmann syndrome cases (Table 1). Similar to patients with *PROKR2* mutations, *Prokr2*$^{-/-}$ mice exhibit olfactory bulb hypoplasia, hypogonadotropic hypogonadism, and a lack of GnRH neurons in the hypothalamus.[25] Likewise, *Prok2*$^{-/-}$ mice fail to enter puberty, have low gonadotropin levels, and have a significant decrease in hypothalamic GnRH neurons.[25, 26] Interestingly, GnRH neurons in *Prok2*$^{-/-}$ mice were able to cross the cribriform plate (a horizontal plate of the ethmoid bone) to enter the central nervous system during embryonic development, but the neurons did not migrate into and populate the hypothalamus.[24,26]

Human mutations in *PROK2* and *PROKR2* have been found in the heterozygous, homozygous, or compound heterozygous state.[26–30] Frameshift mutations that inactivate PK2 have been reported in sporadic cases of Kallmann syndrome[28] and in families with a history of Kallmann syndrome or normosmic IHH.[26,30] Three siblings (two brothers with Kallmann syndrome and a sister with normosmic IHH) have been identified who have a homozygous deletion in the *PROK2* gene.[26] The frameshift mutation introduces a premature stop codon, which results in the production of a truncated PK2 protein that lacks the cysteine-rich domains that are critical for the protein's biological activity.[31] A single amino acid substitution in PK2 (Arg73Cys) that greatly reduces activation of PK-R2-mediated stimulation of calcium signaling is predicted to disrupt a disulfide bond. This substitution has been identified in both the homozygous and the heterozygous state in patients with Kallmann syndrome.[28]

Many of the mutations identified in *PROKR2* map to the highly conserved transmembrane domains of the receptor encoded by this gene. In a study of 192 patients with Kallmann syndrome, 10 mutations in *PROKR2* were identified,[27] five (50%) of which resulted in single amino acid substitutions in the transmembrane domains (Leu173Arg, Trp178Ser, Pro290Ser, Met323Ile, and Val331Met). Trp178 and Pro290 are the most conserved amino acids in transmembrane domains four and six, respectively. *In vitro* studies have shown that substitution of Leu173, Trp178, and Pro290 in *PROKR2* impairs the cell surface targeting of the receptor, probably because the receptor protein is incorrectly folded. Calcium signaling by these mutated receptors is equally impaired.[29,32] Other mutants with amino acid substitutions in the first, second and third intracellular loops, or in the carboxyl tail of PK-R2 have similarly impaired calcium signaling but normal expression levels and cell surface targeting. These mutants probably have impaired G-protein coupling.[27,29,32]

Interestingly, in mice, the IHH phenotype has been reported only in those homozygous for the *Prok2* deletion, which suggests that one normal allele may compensate for the inactivity of the other. Similarly, homozygous mutations in *PROK2*[26,29] or *PROKR2*[30] have been found in patients with Kallmann syndrome who have asymptomatic parents or other family members

with heterozygous mutations of this ligand or receptor. The apparent requirement of two mutant alleles for the phenotypic manifestation raises the possibility that an additional mutation may be present in patients with Kallmann syndrome in whom only a single heterozygous mutation in *PROK2* or *PROKR2* has been identified to date.

CHD7

The gene *CHD7* encodes chromodomain-helicase-DNA-binding protein 7 (CHD-7). *CHD7* is expressed in olfactory epithelium, the hypothalamus and the pituitary gland, which suggests that the encoded protein may have a role in olfactory bulb and GnRH neuronal development. Mutations in *CHD7* are predicted to account for 6% of all IHH cases (Table 1).[33] These mutations are hypothesized to be involved in the pathogenesis of IHH by disruption of GnRH neuronal development or migration. Mutations in *CHD7* have been found in patients with CHARGE syndrome, a multisystem disorder that may include IHH. Furthermore, seven mutations in *CHD7* were recently identified in patients with sporadic, normosmic IHH or Kallmann syndrome who were not diagnosed as having CHARGE syndrome.[33] Three of these mutations affect domains critical for chromatin remodeling and transcription regulation by CHD-7. These mutations are believed to result in a milder form of CHARGE syndrome that manifests as normosmic IHH or Kallmann syndrome.

Regulation of GnRH secretion

KISS1 and KISS1R

The reproductive roles of the G-protein-coupled KiSS-1 receptor (also known as GPR54, encoded by *KISS1R*) and its endogenous ligand, kisspeptin 1 (encoded by *KISS1*) were revealed in 2003 when inactivating mutations in the KiSS-1 receptor were found in the homozygous state in members of two large, consanguineous families with a history of normosmic IHH.[34,35] Subsequent studies have shown that both the ligand and receptor are expressed in areas of the hypothalamus that control reproduction.[36] Furthermore, centrally or peripherally injected kisspeptin 1 results in a robust stimulation of GnRH and gonadotropin secretion in the rodent[36–38] and primate[39] and accelerates puberty in prepubertal rodents.[40] In fact, kisspeptin 1 is recognized as the most potent regulator of GnRH secretion in humans and animal models. Kisspeptin 1 was identified by three independent groups in 2001 as a 54-amino acid peptide —kisspeptin 54—which corresponds to residues 68–121 of the *KISS1* gene product; however, shorter peptides of kisspeptin also show biological activity.[41–43]

In rodents, the hypothalamic regions with the highest levels of kisspeptin-expressing neurons are the arcuate nucleus and the anteroventral periventricular nucleus. Kisspeptin 1 expression increases at the time of puberty in both the arcuate and the anteroventral periventricular nuclei. Levels in the latter are significantly higher in female rodents.[44,45] Migration of GnRH neurons and GnRH content in the hypothalamus of mice with targeted disruption of *KISS1R* is normal. The hypothalamic–pituitary axis of these mice is functional, responding with robust luteinizing hormone secretion after GnRH treatment, which suggests that GnRH is the mediator of the stimulatory effects of kisspeptins on gonadotropin secretion.[46] Indeed, *Kiss1r*$^{-/-}$ mice have underdeveloped gonads, low gonadotropins and steroid hormone levels, and incomplete gametogenesis.[35,47] *Kiss1*$^{-/-}$ mice have a similar phenotype, which suggests that kisspeptins are the only physiological ligands of the KiSS-1 receptor.[48]

Inactivating mutations in *KISS1R* show an autosomal recessive pattern of transmission. Mutations in *KISS1R* represent about 5% of cases of normosmic IHH (Table 1). In 2003, de Roux *et al.* reported a mutation of *KISS1R* in a family with individuals with normosmic IHH.[34] This deletion mutation eliminates most of the third cytoplasmic loop of the KiSS-1 receptor. Loss of this loop is predicted to impair the receptor's G-protein coupling even if the receptor

is correctly localized in the membrane. In a different family with individuals with normosmic IHH, a single amino acid substitution mutation (Leu148Ser) of the KiSS-1 receptor was identified.[35] This substitution is located near the DRW(Y) motif, a motif that has an important role in regulating the activation and inactivation of many G-protein-coupled receptors.[49,50] Another single amino acid substitution of the KiSS-1 receptor (Leu102Pro) identified in patients with IHH is located in the first extracellular loop of the receptor. The mutation decreases the expression of the receptor and impairs its signaling ability.[51]

A compound heterozygous mutation identified in a patient with IHH included an insertion of a stop codon at 331Arg in one allele and the replacement of the normal stop codon by an arginine in the other allele (X399Arg). The introduction of a stop codon at 331Arg is expected to generate a truncated KiSS-1 receptor. On the other hand, elimination of the normal stop codon might result in receptor misfolding. Accordingly, *in vitro* studies showed impaired function of both the Arg331X and X399Arg mutant KiSS-1 receptors.[35] Another pair of compound heterozygous mutations (Arg297Leu and Cys223Arg) was identified in a boy with hypogonadism. Cys223 is a highly conserved amino acid located at the beginning of the third intracellular loop of the KiSS-1 receptor. Accordingly, receptor signaling by this mutated protein is profoundly impaired. Although the mutation in the other allele—Arg297Leu—only slightly decreased the activity of the KiSS-1 receptor, the combination of the two mutated alleles was enough to cause hypogonadism.[52]

The key role of the KiSS-1 receptor in the regulation of the onset of puberty was recently reinforced when the first identifiable genetic cause of central precocious puberty was recognized as a gain-of-function mutation in the receptor.[53] The gain-of-function in this case was not achieved by constitutive activation of the KiSS-1 receptor. Instead, the apparent 'activation' of the receptor was the result of a reduced rate of receptor desensitization. Mutations in kisspeptin 1 might be expected to alter reproductive function in a similar fashion to those in the KiSS-1 receptor; however, no reports of kisspeptin mutations associated with IHH have been published to date.

LEP and LEPR

Leptin, encoded by *LEP*, is a fat-derived hormone that regulates food intake, energy expenditure and reproduction at the hypothalamic level. Exogenous administration of leptin accelerates puberty in mice and normalizes reproductive deficiencies in leptin-null (*ob/ob*) mice, which suggests that leptin may be a link between body fat and reproductive capability.[54,55] Accordingly, loss of body fat owing to starvation or excessive exercise is known to suppress reproduction and results in amenorrhea and infertility.[56,57] Likewise, inactivating mutations in *LEP*[58] or the gene encoding its receptor, *LEPR*,[59] have been found in patients with severe obesity and hypo-gonadotropic hypogonadism. These inactivating mutations account for less than 5% of normosmic IHH and have an autosomal recessive pattern of transmission (Table 1). The central role of leptin in these cases is highlighted by the recovery of gonadotropin secretion and menstrual cycles after treatment with recombinant leptin in females with amenorrhea due to congenital leptin deficiency[60] or hypothalamic amenorrhea.[61]

In humans, leptin has a permissive role in the control of reproduction, being necessary but not sufficient for the onset of puberty and maintenance of fertility. Evidence from studies of animal models points to a role for kisspeptin 1 in the reproductive effects of leptin.[62]

TAC3 and TACR3

Neurokinin B (NKB), which is encoded by *TAC3*, is a member of the substance-P-related tachykinin family. NKB is expressed in the arcuate nucleus and its receptor is expressed in

GnRH neurons of rodents, which suggests it has a possible role in the regulation of GnRH secretion.[63] The NKB receptor, NKR (also known as NK-3R) is encoded by *TACR3*. This receptor is a member of the rhodopsin family of G-protein-coupled receptors.

A recent genome-wide single nucleotide polymorphism analysis identified homozygous mutations in *TAC3* or *TACR3* that segregated with the IHH phenotype in four (of nine) unrelated consanguineous families. In one family, a Met90Thr amino acid substitution of NKB affected individuals homozygous for the mutation but not those who were heterozygous. This mutation is located within the canonical tachykinin motif in the carboxyl terminus of the mature ligand. The tachykinin motif is predicted to undergo post-translational amidation for full activation of NKB.[63] *In vitro* studies showed that the stimulation of NKR by NKB is markedly impaired by the Met90Thr substitution.[63]

Two mutations found in *TACR3* replace highly conserved amino acids located in the first (Gly93Asn) or sixth (Pro353Ser) transmembrane domain of NKR. The Gly93Asn mutation was found in all affected members of one family, whereas the Pro353Ser mutation was found in all affected members of two other families.[63] *In vitro* studies showed that these two mutations impair the ability of NKR to activate signal transduction.[63]

Taken together, these results strongly suggest that NKB and NKR have important roles as central regulators of reproductive capability. While the underlying mechanism has not been established, it probably involves the regulation of GnRH secretion, perhaps via interactions with the kisspeptin 1–KiSS-1 receptor system given the co-expression of NKB with kisspeptin in neurons in the arcuate nucleus of the hypothalamus.[64]

PCSK1

Neuroendocrine convertases (also known as prohormone convertases) are enzymes that process larger, usually inactive, precursor peptides to release bioactive fragments. For example, the pro-opiomelanocortin gene product is processed by neuroendocrine convertase 1 (NEC 1; encoded by *PCSK1*) in the corticotroph to produce adrenocorticotropic hormone and lipotropin and by neuroendocrine convertase 2 in the hypothalamus to produce melanocyte-stimulating hormone and endorphin. The first report of a patient with congenital NEC 1 deficiency associated with obesity and hypogonadotropic hypogonadism was published in 1995.[65] A compound heterozygous mutation in *PCSK1* was later identified in this patient in which a Gly483Arg substitution impairs the maturation of the inactive NEC 1 propeptide so that the propeptide is trapped in the endoplasmic reticulum. The second mutation causes a frameshift and the introduction of a premature stop codon in the catalytic domain of the enzyme.[66]

Only two other cases with a similar phenotype associated with *PCSK1* mutations have been identified in humans. A compound heterozygous mutation (Glu250X and Ala213del) was identified in a female infant. Glu250X is predicted to truncate the protein within its catalytic domain, whereas the mutation in the other allele (Ala213del) eliminates a highly conserved alanine near His208, a residue known to be critical for catalytic activity.[67] The second case involved a 6-year-old boy with a homozygous Ser307Leu substitution. This mutation is also within the catalytic domain and severely impairs the catalytic activity of the enzyme.[68] On the basis of phenotypic similarities, infertility is expected in these two patients once they reach pubertal age. Accordingly, mice homozygous for an Asn222Asp NEC 1 substitution, which is also within the catalytic domain of the enzyme, are obese and have decreased fertility.[69] Although no reports have been published on the molecular mechanisms by which mutations in *PCSK1* cause hypogonadism, the impairment of GnRH prohormone precursor processing is probably involved in these cases.

GnRH action: *GNRHR*

The GnRH receptor (encoded by *GNRHR*) is a 328 amino acid protein that belongs to the rhodopsin family of G-protein-coupled receptors. Activation of the GnRH receptor increases calcium mobilization and stimulates influx of extracellular calcium. This increase in intracellular calcium induces pituitary luteinizing hormone and follicle-stimulating hormone secretion.[70] Germ-line mutations in *GNRHR* were among the first genetic mutations identified in patients with IHH.[71] During the past 10 years, at least 19 additional loss-of-function mutations in the GnRH receptor have been identified in patients with IHH.[72] Large-scale screening indicates that *GNRHR* mutations account for 3.5–16% of sporadic cases of normosmic IHH and up to 40% of familial cases of normosmic IHH (Table 1).[72] Inheritance is autosomal recessive and most patients have compound heterozygous *GNRHR* mutations.[70]

All but two known *GNRHR* mutations are missense, leading to single amino acid substitutions. These mutations impair GnRH signaling through loss of receptor expression, ligand binding, G-protein coupling, and/or abnormal intracellular trafficking of the receptor. About 82% of all transmembrane domain mutations cause complete impairment of ligand binding and signaling. Only two of 11 mutations identified in transmembrane domains encode a partially functional receptor; the other nine encode completely inactive receptors. On the other hand, only one of the mutations reported in other domains encodes a completely inactive receptor.

Some *GNRHR* mutations with partial effects on signaling were found in patients with compound heterozygous mutations, such as Gln106Arg–Arg262Gln. Gln106Arg maps to the first extracellular loop of the GnRHR and decreases GnRH binding.[71] The Arg262Gln substitution is located in the third intracellular loop, the main site of G-protein interaction. This mutation impairs signal transduction, suggesting that activation of G proteins is affected. The parents of the affected siblings were phenotypically normal, despite each being heterozygous for one of these substitutions.[73] Functional responses and structure–function relationships of GnRH receptor mutations have been described in detail.[72,74] The reversal of IHH in a patient carrying a homozygous mutation in *GNRHR* has been reported by Pitteloud and colleagues.[75] The reversal of the phenotype after treatment suggests that hormonal replacement may compensate for an underlying genetic abnormality in cases where the mutations result in only partial loss of function.

Conclusions

Mutations in a number of genes have been identified in patients as the primary genetic cause of IHH. These genes encode proteins that regulate GnRH neuronal development, migration from the nasal placode to the hypothalamus, GnRH secretion, or GnRH action. While some genetic mutations are sufficient to cause IHH, other cases are predicted to result from the combination of more than one genetic abnormality. In such cases, the partial loss of function caused by one genetic mutation may not manifest with a reproductive phenotype, whereas the presence of a second mutation overwhelms the ability to compensate for the effects of the first mutation, resulting in IHH. Many of the genetic causes of IHH have been identified only recently and their individual and/or combined roles in the regulation of reproduction are not yet completely understood. Despite these recent advances, the genetic basis of the vast majority of cases of IHH remains unknown, and much room remains for further discovery.

Key points

- The genetic basis of the vast majority of cases of idiopathic hypogonadotropic hypogonadism (IHH) remains unknown

- IHH with anosmia (Kallmann syndrome) is caused by the defective developmental migration of gonadotropin-releasing hormone (GnRH) and olfactory neurons; associated genes encode proteins involved in this migration
- Molecular mechanisms that underlie IHH in patients with a normal sense of smell are diverse and may involve genes that regulate development and/or GnRH secretion or action
- A considerable number of IHH cases probably involve mutations in more than one gene; that is, these cases are polygenic
- Sex-associated factors also contribute to the IHH phenotype

Review criteria

Literature searches of Google Scholar and MEDLINE databases from 1990 to 2009 were based on the keywords: “IHH”, “hypogonadism”, “Kallmann syndrome”, “anosmia”, “FGFR1”, “KAL1”, “KAL2”, “GnRH”, “GPR54”, “kisspeptin”, “metastin”, “PROK2”, “PROKR2”, “leptin”, “leptin receptor”, and “prohormone convertase”.

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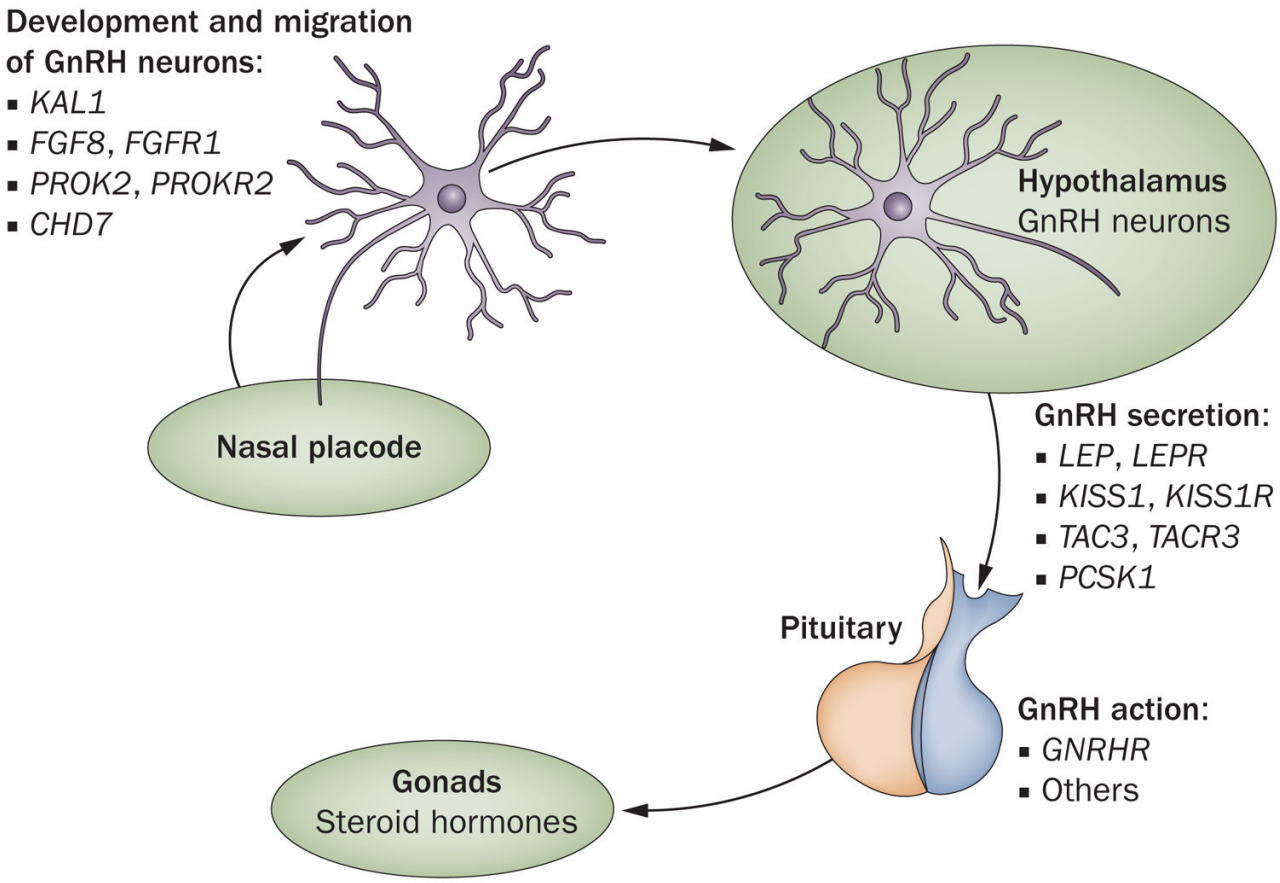

Figure 1.

The genetic basis of idiopathic hypogonadotropic hypogonadism. The mechanisms that underlie hypogonadotropic hypogonadism involve mutations in many genes. Some of these genes encode proteins that regulate GnRH neuronal migration, other genes encode proteins that regulate GnRH secretion or GnRH action. Abbreviation: GnRH, gonadotropin-releasing hormone.

Table 1

The genetic basis of idiopathic hypogonadotropic hypogonadism

Genes related to IHH	Gene product	Mode of inheritance	Cases for this specific form of IHH (%)	Cases of IHH overall (%)
Kallmann syndrome ~60% of total				
KAL1	Anosmin 1	X-linked	5–10	3–6
FGFR1	Fibroblast growth factor receptor 1	Autosomal dominant	10	6
FGF8	Fibroblast growth factor 8	Autosomal dominant	<5	<2
PROK2, PROKR2	Prokineticin 2, prokineticin receptor 2	Autosomal recessive	5–10	3–6
CHD7	Chromodomain-helicase-DNA-binding protein 7	NR	10	6
Unidentified	NA	NA	60–75	NR
Normosmic IHH ~40% of total				
GNRHR	Gonadotropin-releasing hormone receptor	Autosomal recessive	16–40	6.5–16
KISS, KISS1R	Kisspeptin 1, KiSS-1 receptor	Autosomal recessive	5	2
TAC3, TACR3	Neurokinin B, Neurokinin B receptor	Autosomal recessive	NR	NR
LEP, LEPR	Leptin, leptin receptor	Autosomal recessive	<5	<2
PCSK1	Neuroendocrine convertase 1	Autosomal recessive	<5	<2
Unidentified	NA	NA	~50	NR

IHH incidence in the population is 1–10 cases in 100,000 births. Patients with Kallmann syndrome have partial or total loss of sense of smell, whereas in normosmic IHH, sense of smell is not affected. In the unidentified group, the genetic basis of the IHH phenotype has not been identified. Abbreviations: IHH, idiopathic hypogonadotropic hypogonadism; NA, not applicable; NR, not reported.