MINIREVIEW

Fertility and Infertility: Genetic Contributions from the Hypothalamic-Pituitary-Gonadal Axis

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INTRODUCTION

Infertility affects approximately 1 in 10 couples. Causes include physical, environmental, and genetic factors, and both partners are equally likely to be affected. It is often difficult to establish a diagnosis for the cause of infertility. "Idiopathic infertility" still predominates as a diagnosis, which reflects the challenges of defining the pathophysiology of infertility in individual couples. Nevertheless, treatment is often successful, using ovulation induction, *in vitro* fertilization, or ICSI (intracytoplasmic sperm injection).

Given the large number of genes that are potentially involved in sex determination, steroidogenesis, and fertility, space limitations preclude a comprehensive review of all genetic abnormalities associated with infertility (*e.g*. chromosomal abnormalities, disorders of steroid biosynthesis, and metabolic disorders). In this review, we have focused primarily on genes involved in the hypothalamic-pituitary-gonadal (HPG) axis. These disorders have provided important insight into the function of the reproductive axis in humans and may point the way toward improved strategies for the diagnosis and treatment of infertility.

Several single-gene disorders affect HPG function and fertility in humans (Fig. 1 and Table 1). Although most of these disorders are relatively rare, they should be considered as causes of infertility for a variety of reasons. First, understanding the pathophysiology of infertility can allow patients to be counseled about their prognosis and the risk of transmitting a condition to their children. Second, treatment can be tailored more appropriately in the context of known hormonal deficits. Finally, it is likely that the cases described to date represent the most severe end of the phenotypic spectrum. Disorders associated with milder phenotypes may be more common and could provide further information about the transcription factors, hormones, and receptors involved in reproduction.

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TRANSCRIPTION FACTORS EXPRESSED THROUGHOUT THE REPRODUCTIVE AXIS: SF-1 AND DAX-1

Two transcription factors, steroidogenic factor-1 (SF-1) and DAX-1, are widely expressed throughout the reproductive axis, including the hypothalamus, gonadotrope cells of the pituitary, gonads, and adrenal gland. Genetic studies, in mice and humans, have shown that both factors play an important role in fertility.

SF-1 regulates the transcription of an array of genes involved in steroidogenesis, male sexual differentiation, and reproduction. Homozygous deletion of the gene encoding Sf-1 in mice results in adrenal and gonadal agenesis, complete XY sex reversal with persistence of Müllerian structures in males, and abnormalities of the hypothalamus and pituitary gonadotropes. The role of SF-1 in humans is less clear. We have recently found a heterozygous missense mutation in the DNA-binding domain of SF-1 in a patient with complete XY sex reversal and adrenal failure (our unpublished data). Gonadotropin release was preserved, but testicular development was severely affected. No SF-1 (*FTZF1*) mutations have yet been reported in genotypic females, where sex reversal would not be expected. Identifying such patients could provide fascinating insight into the role of SF-1 in ovarian development and function.

Considerably more is known about the role of DAX-1 in humans (1). Mutations in the gene encoding DAX-1, *AHC* (Xp21), cause X-linked adrenal hypoplasia congenita. Hemizygous males develop primary adrenal failure in infancy or childhood. Although the HPG axis

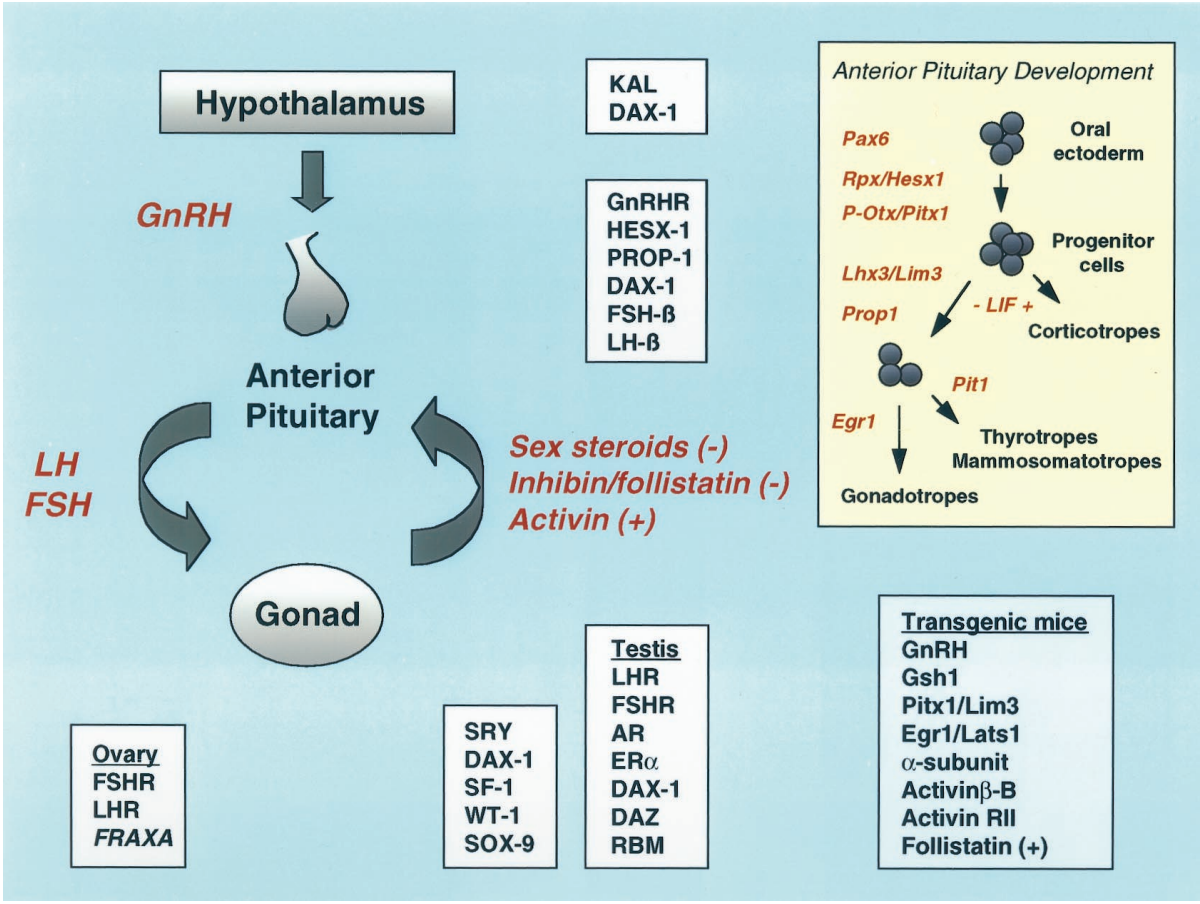

Fig. 1. Schematic Representation of the Hypothalamic-Pituitary-Gonadal Axis (*main figure*) and Anterior Pituitary Development (*inset*)

Mutations in genes reported to affect fertility or gonadal development in humans are shown in *white boxes*.

appears to be intact in early life, hypogonadotropic hypogonadism (HHG) develops later in life, and these boys fail to enter puberty. There is evidence for defective production of hypothalamic GnRH as well as impaired pituitary responses to exogenous GnRH. DAX-1 is also expressed in Sertoli cells. Targeted disruption of the *Ahch* gene (which encodes Dax-1) causes disordered spermatogenesis and infertility in mice (2). It is not yet known whether exogenous gonadotropins will be effective for inducing spermatogenesis in patients with DAX-1 mutations.

The majority of *AHC* mutations truncate the carboxy terminus (carboxy-terminal P5) of the DAX-1 protein. This region is critical for functional activity of the transcription factor. Genotype-phenotype correlations are limited at present. Most functional studies have shown that DAX-1 represses the transcriptional activation of many genes that are regulated by SF-1. Such repressor activity is seemingly paradoxical, considering that the adrenal and reproductive failure seen in patients with DAX-1 mutations resembles many of the features of mice with Sf-1 mutations. However, the repressive activity of DAX-1 is consistent with the sex reversal that is seen in males with duplication (overexpression) of the *AHC* (DAX-1) locus. Thus, DAX-1 appears to function in a dosage-sensitive manner: high levels of DAX-1 impair testis determination, but spermatogenesis is impaired in the absence of DAX-1. Moreover, although DAX-1 was originally postulated as an ovarian determination gene, female *Ahch* knockout mice develop ovaries and are fertile (2).

GnRH

Disorders affecting the production or function of GnRH can result from abnormal neuronal migration, defective synthesis and release of GnRH, or mutations in the GnRH receptor.

GnRH-releasing neurons originate in the olfactory placode and migrate to the fetal hypothalamus. This observation explains the association of HHG with anosmia (absent sense of smell) in Kallmann syndrome. Unilateral renal agenesis and neurological features (*e.g.* synkinesia) can also occur in the X-linked form of this condition, which results from mutations in *KAL*. This gene encodes an extracellular matrix glyco-

Table 1. Single Gene Disorders in the Hypothalamic-Pituitary-Gonadal Axis Resulting in Impaired Fertility

Gene	Locus	Product	Reported Mutations (number/families)	Phenotype	
				Sex	Features
AHC (DAX1)	Xp21	Orphan nuclear hormone receptor	57/66	M	Adrenal failure, HHG (hemizygous)
KAL	Xp22	Extracellular matrix protein	25/34	M	HHG, anosmia +/− unilateral renal agenesis, synkinesia (hemizygous)
GNRHR	4q21	G-protein coupled receptor	4/4	M	Delayed puberty, hypogonadism, severe oligospermia
				F	Delayed puberty, variable thelarche, amenorrhea
HESX1	3p21	Paired-like homeodomain TF	1/1	M/F	Septo-optic dysplasia, panhypopituitarism
PROP1	5q35	Paired-like homeodomain TF	6/24	M/F	Variable HHG; GH and TSH deficiency
FSHβ	11p13	Glycoprotein hormone	3/5	M	Normal/delayed puberty, hypogonadism, azoospermia
				F	No thelarche, primary amenorrhea
FSHR	2p21-p16	G-protein coupled receptor	2/28	M	Variable hypogonadism and mild oligospermia
				F	Variable puberty; primary or secondary amenorrhea
LHβ	19q13	Glycoprotein hormone	1/1	M	Delayed puberty, azoospermia (arrested)
LHR	2p21	G-protein coupled receptor	10/10	M	Range: complete feminization/ hypospadias/micropenis, pubertal failure, azoospermia
				F	Normal puberty; amenorrhea or oligomenorrhea
ERα	6q25	Nuclear hormone receptor	1/1	M	Normal puberty; prolonged linear growth, subnormal sperm viability
AR	Xq11–q12	Nuclear hormone receptor	>200/>300	M	Range: complete feminization/ hypospadias/infertility

HHG, hypogonadotropic hypogonadism; TF, transcription factor. Contiguous gene deletion syndromes (*AHC*, *KAL*), polymorphic variants (*LHβ*) and activating mutations (*LHR*, *FSHR*) not included.

protein, anosmin-1, which is involved in neuronal growth and migration. The clinical features of patients with *KAL* mutations are highly variable, even within the same kindred, suggesting that modifier genes may compensate for these mutations or that epigenetic phenomena influence phenotypic expression (3).

Analyses of pedigrees with familial GnRH deficiency suggest that X-linked forms of inheritance are relatively rare compared with autosomal-dominant and -recessive forms of transmission. However, autosomal genes involved in neuronal migration and other aspects of GnRH production have not been identified in humans. One candidate gene is *GNRH* itself, since *hpg/hpg* mice (which have a GnRH gene deletion) have recessively inherited HHG. In fact, hypogonadism has been described in patients with 8p deletions involving the *GNRH* locus, but no abnormalities specifically within the human *GNRH* gene have been reported.

Several families with compound heterozygous mutations in the GnRH receptor have been described recently (4, 5). These receptor mutations reduce GnRH binding and/or activation of inositol triphosphate or phospholipase C. Clinical features range from complete to partial HHG, even within the same kindred. Some patients have little spontaneous gonadotropin release, whereas others have normal basal gonadotropin concentrations (3.0 IU/liter), but pulses have reduced amplitude. The gonadotropin response to GnRH stimulation is also variable. Mutations in the GnRH receptor should therefore be considered a cause of HHG and are not precluded by the presence of detectable basal gonadotropins.

ANTERIOR PITUITARY DEVELOPMENT

Anterior pituitary development is regulated by a large number of transcription factors with complex spatial and temporal interactions (Fig. 1, *inset*). Much has been learned about the role of these factors from

transgenic models. To date, mutations affecting gonadotrope function have been found in two human homologs, *HESX1* and *PROP1*. *Hesx1* is a homeobox gene involved in forebrain and pituitary development. Mice lacking *Hesx1* exhibit variable anterior central nervous system defects and pituitary dysplasia. A homozygous R53C missense mutation in *HESX1* has been reported in two children with familial septo-optic dysplasia and panhypopituitarism (6). This mutation reduces the ability of HESX-1 to bind DNA and confirms that *HESX1* is involved in early pituitary development in humans.

A homozygous missense mutation (S83P) in the gene *Prop1* (prophet of Pit-1) causes GH, PRL, and TSH deficiency in Ames dwarf (*df*) mice. Gonadotrope differentiation is also impaired, and homozygous females and most males are infertile. Mutations in the human *PROP1* gene have now been identified in more than 20 families. Mutations are clustered within the PROP-1 homeodomain and reduce binding affinity and transcriptional activation of the transcription factor (7). The delA301G302 mutation is particularly common, even in unrelated kindreds, and may represent slipped strand mispairing in this AG repeat region. Some patients with *PROP1* mutations demonstrate HHG and pubertal failure. Others progress through puberty spontaneously but develop hypogonadism or amenorrhea when older. Such phenotypic variability can be seen within families with the same mutation. The interaction of these transcription factors with potential modifiers (*e.g*. LIF, leukemia inhibitory factor) is unclear, as is the role of other gonadotrope-specific transcription factors (*e.g*. EGR-1, SF-1, and DAX-1) in humans. Given the increasing number of transcription factors that are being identified as playing a role in pituitary development and gene expression, one can anticipate the description of additional genetic defects in the future.

GONADOTROPINS AND THEIR RECEPTORS

The gonadotropins are heterodimers consisting of specific β-subunits that are noncovalently bound to a common α-subunit. No human α-subunit mutations have been reported, although dysfunction of all glycoprotein hormones (TSH, hCG) would be expected based on targeted disruption of this gene in mice. Because hCG plays an essential role in the maintenance of pregnancy in humans (but not in rodents), α-subunit mutations may not be seen in humans. A number of mutations in the *FSH*β and *LH*β genes and receptors have been described and have highlighted differences in gonadotropin action between men and women (Fig. 2).

Mutations in the *FSH*β gene have been reported in three women who presented with delayed puberty, lack of breast development, and primary amenorrhea. Normal primordial follicles were detected and, in two cases, follicular maturation, ovulation, and fertility were achieved after treatment with exogenous FSH. Coexpression of mutant *FSH*β with the α-subunit gene revealed dramatically reduced FSH, suggesting that these mutations interfere with the synthesis and stability of the heterodimer complex (8).

A similar, although less severe, phenotype has been reported in 22 Finnish women, who are homozygous for a missense mutation (A189V) in the FSH receptor (9). Variable pubertal failure and primary or secondary amenorrhea were seen in these women. This mutation, in the extracellular domain of the receptor, reduces receptor binding to FSH. These features mirror those in female FSHβ and FSH receptor knockout mice, where a block in folliculogenesis is seen (10). Taken together, these reports underscore the importance of FSH for granulosa cell estrogen production, follicular maturation, and fertility. Furthermore, a report of a compound heterozygous FSH receptor mutation in a woman with secondary amenorrhea supports the idea that subtler phenotypes can result when partial loss of function occurs (11).

The role of FSH in spermatogenesis remains unclear. Male FSHβ and FSH receptor knockout mice are fertile, despite having reduced testicular size and partial spermatogenic failure (10). Similarly, five Finnish men with the FSH receptor mutation described above (A189V) did not have absolute azoospermia (12). Rather, there was a variable reduction in testicular volume, and a range of spermatogenic failure was seen. These reports suggest that, in contrast to female gametogenesis, FSH is not absolutely required for spermatogenesis. Testosterone may play a compensatory role in supporting spermatogenesis in the absence of FSH in these cases.

This view has been challenged somewhat by two recent reports of azoospermic men who have homozygous mutations in the FSHβ gene. In one case, puberty was delayed, testosterone concentrations were low, and full virilization was not achieved. These features could have contributed to the lack of spermatogenesis (13). In the other case, puberty had occurred normally several years before investigation, testosterone was within the normal range, yet no spermatozoa were detected in ejaculates. Testicular biopsy showed spermatogenic arrest (14). These findings suggest that the phenotypic spectrum of FSHβ or FSH receptor mutations is variable in men. Additional cases of naturally occurring human FSHβ and FSH receptor mutations will help to clarify the role of FSH in spermatogenesis.

Only one *LH*β gene mutation has been reported, in a male with pubertal delay, low testosterone, and arrested spermatogenesis. This homozygous missense mutation (Q54R) preserved hormone synthesis and immunoreactivity, but prevented its binding to the LH receptor (15). Long-term treatment with hCG resulted in testicular enlargement, virilization, and increased sperm count, but fertility was not achieved. The normal development of male external genitalia in this case

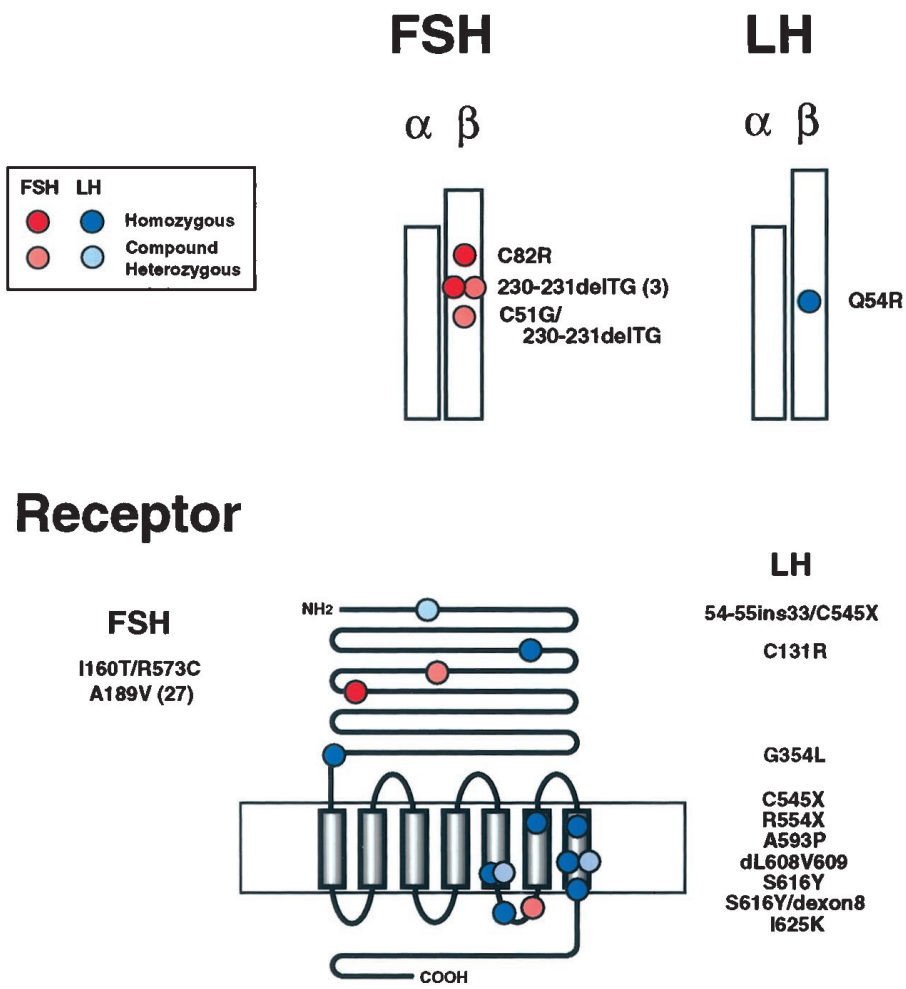

Fig. 2. Reported Mutations in the FSH and LH β-Subunits (*top panel*) and Inactivating Mutations of the FSH/LH Receptor (*composite diagram, lower panel*)

For clarity, activating mutations of the LH receptor and FSH receptor are not depicted.

may reflect the *in utero* action of hCG on the LH receptor. This action of hCG might be expected to generate testosterone during the critical period of genital development. This scenario contrasts with the absent or incomplete genital development that is usually seen in males with inactivating mutations of the LH receptor. However, a broad spectrum of phenotypes is also associated with LH receptor mutations. Two phenotypically milder LH receptor mutations have been reported in patients with micropenis (S616Y, I625K), absent puberty, and infertility (S616Y). Testicular biopsy in one patient showed no mature Leydig cells and an arrest of spermatogenesis at the spermatid stage (16). These milder mutations are located within the carboxy-terminal portion of the seventh transmembrane domain (Fig. 2), and functional studies have demonstrated a relationship between residual receptor activity and clinical phenotype (16). The LH receptor is therefore another candidate gene for infertility in males.

Several women with homozygous LH receptor mutations have now been identified in these families (17). All had amenorrhea or oligomenorrhea despite normal pubertal development. This finding highlights the role of the LH receptor in ovulation and suggests that receptor mutations could also occur in a subset of women with infertility.

Activating mutations also occur in the LH receptor and cause male-limited precocious puberty. These mutations, located in the transmembrane domain, appear to induce receptor coupling to G proteins, even in the absence of hormone. These activating mutations do not appear to alter fertility, but a subset of the mutations may predispose to Leydig cell neoplasia.

GONADAL DEVELOPMENT AND GAMETOGENESIS

Testis determination and development require the interaction of a complex cascade of genes, including *SRY*, *WT1*, *FTZF1*, and *SOX9*. Mutations in these genes generally cause marked testicular dysfunction,

resulting in sex reversal or genital ambiguity, as well as infertility. Gametogenesis itself requires the normal function of many additional genes, as demonstrated by the large number (>30) of transgenic animals with spermatogenic failure. Many of these are relevant in humans [*e.g*. cAMP response element modulator (CREM)]. In addition, deletions of two gene families (*RBM* and *DAZ*) on the Y chromosome, which encode putative RNA-binding proteins, have been found in a significant proportion of men with azoospermia.

Although specific ovarian determining genes remain elusive, a number of factors have been implicated in germ cell migration and growth [*e.g*. c-*kit*, stem cell factor (SCF), transforming growth factor-β], follicular development [including Egr-1, growth and differentiation factor (GDF)-9, and connexin 37], and the regulation of follicle survival/apoptosis (*e.g*. *Bcl-2*, *Bax*). In humans, premature ovarian failure can be associated with fragile X (*FRAXA*) premutations or deletions of several X chromosome loci (*e.g*. *POF1,* Xq21.3-q27; and *POF2*, Xq13.3-q21.1). Many of the genes involved in gametogenesis and the regulation of cell survival remain to be characterized.

SEX STEROID RECEPTORS

Androgen and estrogen receptor mutations can potentially influence fertility, by impairing sex steroid action in the gonad, as well as altering control of gonadotropin production. More than 200 androgen receptor mutations have been reported to date (see http://www.mcgill.ca/androgendb/). Milder forms of androgen insensitivity can present with infertility alone and usually result from missense mutations in the ligand-binding domain. The androgen receptor is therefore a candidate gene for idiopathic infertility. By contrast, only one human estrogen receptor (α) mutation has been reported. The affected man had normal pubertal development, a sperm count within normal limits, but reduced sperm viability. Of note, a role for estrogen in the regulation of luminal fluid has been proposed based on studies in the male ERα knockout mouse. No estrogen receptor mutations have been found in women, although these remain candidate genes for pubertal failure and infertility.

OTHER MODIFIERS OF THE HPG AXIS

Inhibin, activin, and follistatin have important endocrine and paracrine actions in the HPG axis. Several transgenic models that involve these factors exhibit impaired fertility. Inhibin consists of an α-subunit and one of two distinct β-subunits (βA and βB) and supresses FSH in males and females. Disruption of the α-subunit results in elevated FSH and gonadal stromal tumors, likely reflecting the unopposed actions of activin. The potential impact of inhibin overexpression on fertility is unclear, and its receptor is yet to be characterized. Activin is composed of dimers of the inhibin β-subunits (A, AB, B), and it stimulates FSH. Disruption of the β-B subunit affects female reproduction, whereas β-A subunit disruption is lethal. Deletion of the activin receptor type II (Act R II) causes delayed fertility in males and infertility in females. Finally, overexpression of follistatin, an activin-binding protein, causes impaired fertility in males and females (18) (see Ref. 19 for a review of transgenic animal models in reproductive endocrine research).

CONCLUSIONS AND FUTURE DIRECTIONS

The genetic disorders described here have provided important insight into the function of the HPG axis in humans, but many questions remain. For example, what is the prevalence of these disorders in patients with infertility? Do milder phenotypes exist that may be more common and might provide important information about the structure-function relationships of these proteins? How might knowledge of these disorders alter our approach to patient management, when more advanced techniques, more selective drugs, or even gene therapy become available? Research using transgenic mice is uncovering a host of candidate genes for disorders of fertility. However, the functions of genes in murine models cannot always be extrapolated to humans. The functional roles of many human homologs remain to be explored. In addition, the association of hypogonadism with mutations in other human genes, such as leptin, its receptor, POMC, and prohormone convertase-1, has provided insight into other factors that might regulate reproduction. Finally, although this review has focused primarily on infertility, an increased understanding of reproductive function is also significant for the regulation of fertility and the development of more effective, safe, and accessible approaches to contraception.

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