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Review

Genetics basis for GnRH-dependent pubertal disorders in humans

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ABSTRACT

Human puberty is triggered by the reemergence of GnRH pulsatile secretion, with progressive activation of gonadal function. Several mutations have been identified in an increasing number of genes that influence the onset of puberty. Mutations in *GNRH1*, *KISS1R and GNRHR* genes cause normosmic IHH, interfering with the normal synthesis, secretion or action of GnRH. More recently, mutations in *TAC3* and *TACR3* genes, which encode neurokinin B and its receptor, have been implicated in normosmic IHH, although their precise functions in reproduction remain unclear. Mutations in *KAL1*, *FGFR1*, *FGF8*, *PROK2 and PROKR2* are related to disruption of the development and migration of GnRH neurons, thereby resulting in Kallmann syndrome, a complex genetic condition characterized by isolated hypogonadotropic hypogonadism (IHH) and olfactory abnormalities. Furthermore, mutations in *CHD7* gene, a major gene involved in the etiology of CHARGE syndrome, were also described in some patients with Kallmann syndrome and normosmic IHH. Notably, the evidence of association of some of the genes implicated with GnRH neurons development and migration with both Kallmann syndrome and normosmic IHH, blurring the simplest clinical distinction between ontogenic and purely functional defects in the axis. Digenic or oligogenic inheritance of IHH has also been described, illustrating the extraordinary genetic heterogeneity of IHH. Interestingly, rare gain-of-function mutations of the genes encoding the kisspeptin and its receptor were recently associated with central precocious puberty phenotype, indicating that the premature activation of the reproductive axis may be also caused by genetic mutations. These discoveries have yielded significant insights into the current knowledge of this important life transition.

Contents

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1. Introduction

Gonadotropin-releasing hormone (GnRH) is the master hormone of the reproductive endocrine system, largely controlling the secretion of luteinizing hormone (LH) and follicle stimulating hormone (FSH) from pituitary gonadotrope cells. These gonadotropins then evoke steroidogenesis and gametogenesis from the gonads, culminating in secondary sexual features development and fertility.

The human GnRH is a decapeptide produced by a small number of GnRH neurons in the preoptic area (Kakar et al., 1992). The GnRH neurons originate in the olfactory placode and undergo a remarkable axophilic migration along the scaffold of olfactory, vomeronasal, and terminal nerves into the forebrain (Kakar et al., 1992; Gonzalez-Martinez et al., 2004). Ultimately, the GnRH neurons dissociate from their olfactory guiding fibers to reach the preoptic area, where their axons extend into the median eminence. These complex development events are tightly regulated by specific spatiotemporal expression patterns of growth factors, adhesion molecules and/or diffusible attractants and repellents (Gonzalez-Martinez et al., 2004).

Human genetics has been a powerful contributor to the discovery of molecular elements critically involved in the central control of reproduction, identifying several molecules that are essential for the embryonic migration of GnRH neurons as well as for the regulation and action of the hypothalamic GnRH. Indeed, studies in patients with Kallmann syndrome, normosmic isolated hypogonadotropic hypogonadism (IHH) and, more recently, in children with central precocious puberty (CPP) have led to the identification of several gene mutations, underscoring the critical role of new peptides implicated in reproduction (Table 1). In this article, we will review the major genes associated with GnRH-dependent pubertal disorders, including normosmic IHH, Kallmann syndrome and central precocious puberty.

2. Isolated hypogonadotropic hypogonadism

Congenital IHH is characterized by partial or complete lack of pubertal development, secondary to deficient GnRH-induced gonadotropin secretion. The diagnosis is based on the presence of low levels of sex steroids associated with low or inappropriately normal LH and FSH serum levels, with no anatomical lesion in the hypothalamic–pituitary tract and no other pituitary hormone deficiencies (Seminara et al., 2000a). When IHH is associated with olfactory abnormalities, it characterizes Kallmann syndrome (Oliveira et al., 2001). Normosmic IHH is a rare and genetically heterogeneous condition, which occurs most commonly in the sporadic form or, less frequently, inherited as an autosomic recessive trait (Quinton et al., 2001). GnRH receptor inactivating mutations were the first genetic alterations recognized as a monogenic cause of normosmic IHH, although the molecular basis of the majority of IHH cases remained undefined (de Roux et al., 1997). In the last few years, however, a number of neuropeptides and their receptors involved in the control of different stages of GnRH function were implicated in the pathogenesis of normosmic IHH, especially in familial cases. Mutations in *GNRH1*, *KISS1R and GNRHR* genes cause normosmic IHH, interfering with the normal synthesis, secretion or action of GnRH, respectively (de Roux et al., 1997, 2003; Seminara et al., 2003; Bouligand et al., 2009; Chan et al., 2009). Mutations in *TAC3* and *TACR3* genes, which encode neurokinin B and its receptor, expressed in the arcuate nucleus and in the median eminence, have also been recently shown to cause normosmic IHH, although their precise functions in reproduction remain unclear (Topaloglu et al., 2009).

2.1. GnRH receptor

The human GnRH receptor (*GNRHR*) gene, located at 4q13.2-3, encodes a 328 amino acid G protein-coupled receptor with seven transmembrane domains and an extracellular amino terminus, but no intracellular carboxy terminus. Ligand biding results in activation of phospholipase C, with increased inositol triphosphate (IP3) production and intracellular calcium mobilization (Kakar et al., 1992).

Mutations in the *GNRHR* gene were first described by de Roux et al. (1997). To date, approximately twenty different homozygous or compound heterozygous mutations in the *GNRHR* have been reported in patients with sporadic or familial forms of IHH, in an autosomal recessive mode of inheritance (de Roux et al., 1997; Soderlund et al., 2001; Layman et al., 1998; Kottler et al., 1999; Costa et al., 2001; Silveira et al., 2002; Seminara et al., 2000b; Meysing et al., 2004; Pralong et al., 1999). Large-scale screening revealed that *GNRHR* mutations account for 3.5–16% of sporadic cases of normosmic IHH and up to 40% of familial cases of IHH (Beranova et al., 2001).

The mechanisms responsible for the inactivation of the mutant GnRH receptors include defects in the synthesis, trafficking to the cell membrane and/or in internalization, recycling, or degradation of receptors, impaired ligand binding and/or ligand-induced signal transduction, leading to various degrees of LH and FSH deficiency (Conn and Janovick, 2009). The phenotypic spectrum of normosmic IHH patients with *GNRHR* mutations varies from partial to complete hypogonadism (de Roux et al., 1997; Costa et al., 2001; Silveira et al., 2002; Pitteloud et al., 2001). Female patients with complete hypogonadism due to *GNRHR* mutations do not respond to pulsatile GnRH treatment for infertility (Meysing et al., 2004), whereas patients with partial IHH demonstrate dose-dependent responses to pulsatile GnRH in terms of gonadotropin secretion and ovulation (Seminara et al., 2000b; Kottler et al., 1999). 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 (Lin et al., 2006). Pitteloud et al. (2001) reported spontaneous reversal of IHH in a patient carrying a homozygous mutation in GnRH receptor.

2.2. GNRH1

Considering the pivotal role of GnRH in human reproduction, the gene that encodes GnRH is an obvious candidate for explaining normosmic IHH. However, despite the efforts of several teams, no genetic alteration had been reported in this gene in patients with IHH until few months ago, when two independent groups reported homozygous frameshift mutations in the *GNRH1* as a new genetic cause of normosmic IHH.

Bouligand et al. (2009) recently reported a homozygous *GNRH1* frameshift mutation (c.18-19insA) in the amino-terminal region of the signal peptide-containing protein precursor of GnRH in a teenage brother and sister, who had complete normosmic IHH. The severity of gonadotropin deficiency was demonstrated by very low levels of sex steroids and plasma gonadotropins in both siblings. Their unaffected parents and sister were heterozygous and had a normal phenotype, indicating the autosomal recessive transmission. Interestingly, endogenous LH pulsatility was restored by GnRH administration in the affected sister, suggesting a hypothalamic origin of the gonadotropin deficiency and normal responsiveness of the pituitary gonadotrope cells. The frameshift mutation results in an aberrant peptide lacking the conserved GnRH decapeptide sequence, as shown by the absence of immunoreactive GnRH when expressed in vitro. No other mutation in *GNRH1* gene was identified in 145 patients with sporadic IHH in this study.