Review article
http://dx.doi.org/10.3345/kjp.2012.55.1.6
Korean J Pediatr 2012;55(1):6-10

The genes associated with gonadotropin-releasing hormone-dependent precocious puberty

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Received: 18 November 2011, Accepted: 19 December 2011
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Human puberty is a complex, coordinated biological process with multiple levels of regulations. The timing of puberty varies greatly in children and is influenced by both environmental and genetic factors. The key genes of pubertal onset, *KISS1, GPR54, GNRH1* and *GNRHR*, may be major causal factors underlying gonadotropin-releasing hormone-dependent precocious puberty (GDPP). Two gain-of-function mutations in *KISS1* and *GPR54* have been identified recently as genetic causes of GDPP. *GNRH1* and *GNRHR* are also gene candidates for GDPP; however no mutations have been identified in these genes. Presently potential genetic causes like *LIN28B* continues to appear; many areas of research await exploration in this context. In this review, I focus primarily on the genetic causes of GDPP.

Key words: Precocious puberty, Genes, Gonadotropins

Introduction

Puberty is a complex, coordinated biological process that transits an individual from childhood to adulthood. It is initiated by the secretion of gonadotropin-releasing hormone (GnRH) from hypothalamic neurons and secreted GnRH triggers signaling cascades and gonadal activations[1]. GnRH, the key hormone in the onset of puberty, is mediated by kisspeptin activation of the G-protein coupled receptor-54 (*GPR54*), and it exercises major control over secretion of gonadotropins, luteinizing hormone (LH) and follicle stimulating hormone (FSH) from pituitary gonadotrope cell[2]. The secreted gonadotropins evoke steroidogenesis and gametogenesis from the gonads, and ultimately culminate in secondary sexual characteristics.

Precocious puberty is defined as the onset secondary sexual characteristics in girls younger than 8 years old and in boys younger than 9 years old[3]. Children who experience GnRH-dependent precocious puberty (GDPP) demonstrate early activation of the hypothalamic-pituitary-gonadal axis[4]. Since the underlying mechanism of GDPP and normal puberty are identical, GDPP-induced sexual characteristics are appropriate for the child's gender; normal sexual characteristics develop at an abnormally early age.

GDPP occurs more frequently in girls than in boys (approximately 20:1 ratio), and as many as 90% of the female cases are designated as idiopathic[5-7]. On the other hand, organic lesions such as hypothalamic hamartomas, occur more often in boys.

Pubertal timing is regulated by genetic and environmental factors[8,9] and varies among racial groups[10]. In addition, a positive correlation has been shown for the age of menarche between mothers and daughters. Also pubertal development in monozygotic twins exhibits greater concordance than in dizygotic twins[11]. Interestingly, familial GDDP can occur in up to 27.5% of cases[12]. The results of familial segregation analyses indicate potential an autosomal dominant transmission with incomplete sex-dependent penetrance[12]. These findings suggest that genetic factors play important role in GDDP.

KISS1 gene

The *KISS1*-kisspeptin-kisspeptin receptor system functions as a major gatekeeper of the onset of puberty[13,14]. The *KISS1* gene encodes kisspeptin which functions via kisspeptin receptor (*GPR54*). Kisspeptin expression is highest in the arcuate and anteroventral periventricular nuclei, which are known to project into the medial preoptic area. The medial preoptic area contains an abundance of GnRH neurons, which express *GPR54* on the surface[15]. Thus, *KISS1* directly governs the activation of GnRH neurons and downstream cascades and is obvious gene candidate for playing a role in the cause of naturally occurring GDPP[16].

The *KISS1* gene maps to chromosome 1q32-q41 and was identified initially as a tumor metastasis suppressor by the process of subtractive hybridization and differential display following microcell-mediated transfer of chromosome 6 into human melanoma cell lines[17,18]. Later, *KISS1* was shown in many studies to be an important reproductive regulator during the onset of puberty. The gene consists of 3 exons, 2 of which are partially translated exons (exons 2 and 3), that give rise to a 145-amino acid precursor peptide[19]. The precursor peptide is cleaved to 54 (68 to 121) amino acids in length, and can be truncated further to 14 (108 to 121), 13 (109 to 121), or 10 amino acid carboxyl-terminal fragments. The resulting fragments are referred to as kisspeptins, and have been shown subsequently to bind and activate *GPR54* with potency equal to the non-truncated peptide (54 amino acids in length)[20]. In 2003, the product of *KISS1*, kisspeptin was demonstrated to perform a function in the reproductive axis[21]. *KISS1* is a candidate gene for the cause of humans idiopathic hypogonadotropic hypogonadism and GDPP. *KISS1* knockout mouse models have been developed; they demonstrated characteristics of idiopathic hypogonadotropic hypogodadism to varying degrees. Conversely, a specific *KISS1* mutation can lead to prolonged activation of *KISS1*, which eventually results in GDPP. Studies on *KISS1* mutations in patients with GDPP have not provided substantial evidence. Ko et al.[1], Luan et al.[22], and Silveria et al.[23] published the studies on *KISS1* mutations in patients with GDPP. However, Silveria et al.[23] alone identified gain of function *KISS1* mutations (p.P74S and p.H90D). The p.P74S mutation was identified in the heterozygous state from a boy with GDPP. The p.H90D mutation was identified in the homozygous state from 2 unrelated girls with GDDP[23]. Luan et al.[22] and Ko et al.[1] identified 1 potentially meaningful polymorphism (p.P110T), which was detected less frequently in GDDP patients than in controls. Moreover, when subjected to GnRH stimulation test, GDDP patients with the p.P110T polymorphism exhibited lower FSH values than those without p.P110T. Ko et al.[1] suggested that p.P110T may exert a protective effect on pubertal precocity. Thus *KISS1* gene alterations were shown to contribute to GDPP pathogenesis, but further study on *KISS1* gene mutations is required to elucidate GDPP pathogenesis.

GPR54 gene

As noted earlier, *GPR54* (the Kisspeptin receptor) and its ligand, kisspeptin, are major gatekeepers of puberty. The *GPR54* gene is located on chromosome 19p13.3[24] and consists of 5 exons and 4 introns over a length of approximately 3.5 kb. *GPR54* encodes a 7-transmembrane receptor that comprises 398 amino acids and has weak homology with the galanin receptors[24,25]. The *GPR54* receptor is a member of the rhodopsin family of the G protein-coupled receptor superfamily. It was cloned initially in 1999 as an orphan receptor in rat brain[24]. The human *GPR54* receptor is expressed widely in the brain-particularly in the hypothalamus, midbrain, pons, medulla, hippocampus, and amygdale- and in the pituitary, pancreas, placenta, and spinal cord[24,25]. Lower levels of expression were detected in the heart, muscle, kidney, liver, intestine, thymus, lung, and testis[24,25]. *GPR54* inactivation had been discovered previously to causes hypogonadotropic hypogonadism in humans, which motivated a series of pharmacological and physiological studies. These studies confirmed the crucial role played by the kisspeptin/*GPR54* system in hypothalamic-pituitary-gonadal axis activation. In 2003, several loss- of -function mutations in the *GPR54* gene were described in patients with impaired pubertal development. Physiologic studies have demonstrated that binding to the G protein-coupled receptor in the membrane of hypothalamic GnRH neurons enables kisspeptin to function as a powerful stimulant of GnRH secretion[14]. The kisspeptin-*GPR54* system has been implicated in the human GDPP pathogenesis since 2008, when Teles et al.[26] identified activating mutation (p.R386P) in the *GPR54* gene. The p.R386P mutation was identified in the carboxyterminal tail of *GPR54* and responded to kisspeptin exposure with prolonged activation of intracellular signaling pathways, which resulted in significantly increased inositol phosphate accumulation for as long as 18 hours[26]. Recently Bianco et al.[27] learned that the p.R386P mutation yielded prolonged responsiveness to kisspeptin by decreasing *GPR54* degradation, which resulted in a net increase of the mutated receptor being recycled to the plasma membrane. Luna et al.[28] identified 6 *GPR54* polymorphisms in Chinese girls with GDPP. Only one nonsynomious change was found to correlate slightly to the disease[28]. Also, Ko et al.[29] identified 1 known polymorphism in Korean girls with GDPP, but he was unable to determine any disease associations.

Mutation frequency in *GPR54* is a relatively unlikely cause of idiopathic hypogonadotropic hypogonadism (IHH). To date, only 13 mutations have been described[26,30-35]. The occurrence of gain-of-function mutations in the *GPR54* gene is very rare, only 2 mutations have been identified.

GNRH1 gene

The *GNRH1* gene is located on chromosome 8p21.2, spans about 5 kb and contains 3 exons. It encodes the *GNRH1* precursor, which comprises 92 amino acids, and is processed subsequently in *GNRH1*, an active decapeptide[29]. In 2009, Bouligand et al.[36] reported a homozygous *GNRH1* frameshift mutation (c.18-19insA) in the amino-terminal region of GnRH's protein precursor which contains a single peptide that was obtained from a teenage brother and sister, who both had complete normosmic IHH. This report was particularly meaningful because the efforts of several precious teams had never resulted in the identification of alterations in the *GNRH1* gene in patients with IHH. However loss-of-function mutations in *GNRH1* gene have been identified recently as rare genetic causes of normosmic IHH. Although GDPP represents on extreme of pubertal development in contrast to IHH, the activation of *GnRH1* gene to GDPP remains undefined. No reports have shown gain-of-function mutations in the *GNRH1* gene until now, despite the efforts of several teams, including Ko et al.[29], with GDPP patients.

GnRHR gene

The *GnRHR* gene is located on chromosome 4q13.2 and its genomic sequence encompasses about 19 kb. It includes 3 exons and encodes a heptahelical transmembrane domain G protein-coupled receptor that the intracellular carboxyl terminus normally present in other members of this family[37]. In 1997, *GnRHR* inactivating mutations are the first genetic alterations that were recognized as a monogenic cause of normosmic IHH[38], several additional mutations in *GnRHR* have identified to date. Large-scale screening has revealed that *GnRHR* mutations account for about 3.5 to 16% of the sporadic cases of normosmic IHH and up to 40% of familial cases of IHH[39].

Ko et al.[29] tried to identify gain of function mutations in the *GnRHR* gene in 101 Korean girls with GDPP. They identified only 1 novel polymorphism[29]. Thus far, no gain-of-mutations have been reported in the *GnRHR* gene.

LH receptor gene

The LH receptor is coupled to G proteins and thus spans the membrane 7 times. It is characterized by a very large N-terminal in the extracellular domain[40] to which the hormone binds. The LH receptor gene is located on chromosome 2p21[41] and contains 11 exons. The last exon encodes the entire transmembrane and intracellular domains whereas the first 10 exons encode monomers or polymers of leucine-rich repeats that form the extracellular domain[41].

Constitutive activation of the receptor determines Familial Male-Limited Precocious Puberty; it exhibits autosomal dominant familial transmission and is characterized by high testosterone levels with low gonadotropins[42]. Puberty usually occurs between 1 and 4 years of age. Girls with these mutations do not exhibit premature puberty, probably because an increased FSH concentration is necessary to determine ovarian follicle growth and maturation[42].

The FSH receptor gene

The structure of the FSH receptor closely resembles the structure of the LH receptor; the genes are in the same location on chromosome 2p21[43]. The FSH receptor consists of 10 exons, the last of which encodes both the transmembrane and intracellular domains. To date, little is known about activating mutations of the FSH receptor gene.

LIN28B gene

The *LIN28B* gene is located on chromosome, and it was cloned and characterized originally in human hepatocellular carcinoma cells[44]. *LIN28B* is a human homolog of lin-28 of nematode *Caenorhabitidis elegans*; Gain-of-function and loss-of-function mutations in LIN28 result in retarded or precocious development, respectively[45]. The lin-28 family regulates the biogenesis of let-7 microRNA family members, which control the timing of developmental events[45]. Thus *LIN28B* may have a role in human pubertal development and thus, is a candidate gene for precocious puberty. The UKPMC funders group carried out a genome-wide association study on the age of menarche in 4,714 women and reported an association with *LIN28B*[46]. They determined that rs314276 is a single nucleotide polymorphism (SNP) located in intron 2 of *LIN28B*. The SNP resides in a region of high linkage disequilibrium around 200 kb in size that includes the 5' region and the first 3 exons of *LIN28B*[46]. The rs314276 SNP is associated with the timing of pubertal growth and development in both girls and boys[46].

Conclusions

Puberty is a complex multistage process that occurs over a 2- to 3-year period and involves growth acceleration, weight gain and the appearance of secondary sexual physical features. The timing of puberty onset varies greatly among individuals and races, and much of this variation is due to genetic factors. However, the exact causes and mechanisms underlying this variation remain largely unknown. Several genes have been implicated in the pathogenesis of GDPP; the genes are associated with the development and migration of GnRH

neurons, the regulation of GnRH synthesis, secretion and action or gonadotropin cascades. Few genetic causes of GDPP have been identified thus far, but potential genetic causes continue to emerge from research studies, and many areas of research await exploration. In the near future, genetic alterations related to GDPP should be identified individually.

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