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

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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. 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. 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. Children who experience GnRH-dependent precocious puberty (GDPP) demonstrate early activation of the hypothalamic-pituitary-gonadal axis. 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. On the other hand, organic lesions such as hypothalamic hamartomas, occur more often in boys.

Pubertal timing is regulated by genetic and environmental factors and varies among racial groups. 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. Interestingly, familial GDPP can occur in up to 27.5% of cases. The results of familial segregation analyses indicate potential an autosomal dominant transmission with incomplete sex-dependent penetrance. These findings suggest that genetic factors play important role in GDPP.
KISS1 gene

The KISS1-kisspeptin-kisspeptin receptor system functions as a major gatekeeper of the onset of puberty. 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. 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.

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. 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. The precursor peptide is cleaved to 54 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). In 2003, the product of KISS1, kisspeptin was demonstrated to perform a function in the reproductive axis. KISS1 is a candidate gene for the cause of idiopathic hypogonadotropic hypogonadism and GDPP. KISS1 knockout mouse models have been developed; they demonstrated characteristics of idiopathic hypogonadotropic hypogonadism 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. and Silveria et al. published the studies on KISS1 mutations in patients with GDPP. However, Silveria et al. 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 GDPP. Luan et al. 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. 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 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. 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. The human GPR54 receptor is expressed widely in the brain-particularly in the hypothalamus, midbrain, pons, medulla, hippocampus, and amygdala-and in the pituitary, pancreas, placenta, and spinal cord. Lower levels of expression were detected in the heart, muscle, kidney, liver, intestine, thymus, lung, and testis. 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. The kisspeptin-GPR54 system has been implicated in the human GDPP pathogenesis since 2008, when Téles et al. 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. Recently Bianco et al. 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. identified 6 GPR54 polymorphisms in Chinese girls with GDPP. Only one nonsynonymous change was found to correlate slightly to the disease. Also, Ko et al. 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. 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. In 2009, Bouligand et al. reported a homozygous **GNRH1** frameshift mutation (c.18-19insA) in the amino-terminal region of GNRH1’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 normosmic IHH. Approximately 3.5 to 16% of sporadic GDPP cases of normosmic IHH and up to 40% of familial cases of IHH contain 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 normosmic IHH. Approximately 3.5 to 16% of sporadic GDPP cases of normosmic IHH and up to 40% of familial cases of IHH contain 1 novel polymorphism in other members of this family. In 1997, **GnRHR** inactivating mutations were the first genetic alterations that were recognized as a monogenic cause 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. 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. In 1997, **GnRHR** inactivating mutations were the first genetic alterations that were recognized as a monogenic cause of normosmic IHH. 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.

Ko et al. tried to identify gain of function mutations in the **GnRHR** gene in 101 Korean girls with GDPP. They identified only 1 novel polymorphism. The structure of the **FSH receptor** closely resembles the structure of the LH receptor; the genes are in the same location on chromosome 2p21. 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. **LIN28B** is a human homolog of lin-28 of nematode *Caenorhabditis elegans*. Gain-of-function and loss-of-function mutations in **LIN28B** result in retarded or precocious development, respectively. The *lin-28* family regulates the biogenesis of let-7 microRNA family members, which control the timing of developmental events. 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**. 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**. The SNP is associated with the timing of pubertal growth and development in both girls and boys.

**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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