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Genetic etiologies of central precocious puberty

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ABSTRACT

Pubertal onset is a complex process, which is influenced by genetic and environmental factors, such as obesity and endocrine-disrupting chemicals. In addition, the timing of normal puberty varies between individuals and is a highly polygenic trait with both rare and common variants. Central precocious puberty (CPP) is defined as the early activation of the hypothalamic-pituitary-gonadal axis. Genetic factors are suggested to account for 50% to 80% of the variation in puberty initiation, as indicated by the greater concordance of pubertal timing observed in monozygotic twins than in dizygotic twins. Although genetic factors play a crucial role in CPP development, only few associated genes have been identified. To date, four monogenic genes have been identified: *KISS1*, *KISS1R*, *MKRN3*, and *DLK1*. Moreover, mutation prevalence in these genes varies considerably depending on the ethnicity of patients with CPP. This article reviews the current knowledge on the normal pubertal timing and physiology and discusses the CPP-causing genes.

Keywords: Etiology; Puberty; Puberty, precocious

INTRODUCTION

Puberty is considered to be the most characteristic change in the process of development from birth to adulthood, and the period of puberty is often called “an age of storm and stress.” During this period, secondary sexual characteristics are expressed, rapid body growth is achieved, fertilization ability is completed, and many social and psychological changes occur [1]. To date, the factors that trigger puberty are among the mysteries that remain scientifically unsolved.

The beginning of puberty is a complex process which is influenced by genetic and environmental factors, such as obesity and endocrine-disrupting chemicals [2-5]. Metabolic hormones, including leptin and ghrelin, can affect pubertal timing [6]. Recent westernized eating habits and the increase in obesity are thought to be related to the increased incidence of precocious puberty [7]. As the degree of obesity increases, the age of menarche tends to be earlier, and the incidence of precocious puberty in obese children is higher than in children of normal weight [8]. Therefore, alterations in an individual’s nutritional status may affect pubertal onset. Genetic factors are considered play a crucial role in pubertal onset. The fact that this onset differs between races, and the similarity of menarche between mothers and daughters, further

supports the notion that genetic variations affect pubertal onset. Greater concordance of pubertal timing has been found in monozygotic twins than in dizygotic twins [9]. Genetic factors are suggested to account for 50% to 80% of the variation in the initiation of puberty [10,11]. Despite the strong heritability of pubertal timing, our understanding of the underlying genetics remains limited. In this paper, we review the current knowledge on the normal pubertal timing and physiology of puberty, and discuss the central precocious puberty (CPP)-causing genes.

PHYSIOLOGY OF PUBERTY

Sexual development, including breast development or testicular enlargement, is initiated through hypothalamic-pituitary-gonadal (HPG) axis reactivation, after initial activation during the fetal and early postnatal periods [12]. However, before pubertal onset, the negative feedback mechanism acts excessively, and gonadotropins, such as luteinizing hormone (LH) and follicle stimulating hormone (FSH), do not increase despite the low serum sex hormone concentration. Neurons that produce gonadotropin-releasing hormones (GnRH) are suppressed, and inhibitory neurotransmitters, such as opioids, gamma-aminobutyric acid, and melatonin are involved [13].

The HPG axis is reactivated at pubertal onset with the reemergence of pulsatile GnRH release, likely owing to increase in activators, such as kisspeptin signals, which direct GnRH neurons to control pulsatile GnRH release. This occurs via elevation of LH and FSH levels through the pituitary, with downstream activation of sex steroids, including estrogen and testosterone [14]. When puberty begins, LH secretion is initiated at night, which gradually increases in amount and frequency, developing the gonads and promoting sex hormone secretion. During mid-puberty, the pulsatile LH secretion occurs during the day, and the secretion cycle is 90 to 120 minutes [15].

Kisspeptin, a peptide hormone expressed in the hypothalamus, is essential for pubertal onset and progression in mammals [16]. Kisspeptin is encoded by the *KISS1* gene that binds to the *KISS1* receptor (KISS1R). The *KISS1* gene was first discovered in 1996 and has since been mapped to the long arm of chromosome 1q32. The gene consists of three exons, of which two partially translated exons (exons 2 and 3) give rise to a 145 amino acid precursor peptide [17]. Stimulant neuromodulators contain neurokinin B (NKB), which is encoded by the tachykinin 3 (*TAC3*) gene. Mutations involving dysfunction of genes encoding *TAC3* genes (coding NKB) or *TACR3* genes (NKB receptor coding) have contributed to the development of hypogonadism and delayed puberty. As a result, NKB stimulates GnRH release through Kiss1 neurons [18]. Kisspeptin/NKB neurons in arcuate nucleus co-express a third peptide, dynorphin (Dyn). This endogenous opioid peptide inhibits kisspeptin secretion. In animal studies, the administration of Dyn receptor antagonists leads to early pubertal onset [19]. Given the interconnection between these neuromodulators, such as NKB, Dyn, and kisspeptin, called KNDy, the pulsatile GnRH secretion is based on coordinated activity in the KNDy neuronal network, in which NKB stimulates kisspeptin and Dyn exerts an inhibitory action [20].

NORMAL PUBERTAL TIMING

Puberty generally begins between the ages of 8 and 13 in girls and between 9 and 14 in boys; however, the timing varies between individuals [21]. The first pubertal change in boys is testicle enlargement. In general, if the length and volume of the testicles is greater than 2.5 cm and 4 cc, respectively, puberty is considered to have begun. Following this, the scrotum becomes more scrotal, pubic hair develops as the penis develops, and axillary hair commonly appears mid-puberty. Rapid pubertal growth in boys, unlike girls, occurs in stages IV to V of the Tanner stages and occurs about 2 years later than in girls. Moreover, breast tissue development is the first sign of puberty in girls. Then, pubic hair develops within 6 to 12 months, and rapid pubertal growth occurs in Tanner stage II or III, followed by menarche [13]. Menarche, defined as the first menstruation, is a milestone during pubertal development in girls, as it represents the onset of female reproductive capacity. Menarche is a late event during puberty and typically occurs 2 to 2.5 years after pubertal onset. The average age at menarche decreased from 17 years in 1840 to approximately 12 years in 2000 in the majority of developed countries, and has remained stable over the last few decades [22]. Age at menarche varies across countries, generations, and races. In Korea, mean age at menarche decreased from 16.90 years for women born between 1920 and 1925 to 13.79 years for those born between 1980 and 1985, according to the Korean National Health and Nutrition Survey [23].

CENTRAL PRECOCIOUS PUBERTY

CPP, a disease with a striking female predominance, results

from early HPG axis activation, and affected children show pubertal levels of gonadotropins and progressive sexual development, such as breast development and testicular enlargement, before ages 8 and 9 in girls and boys, respectively [21]. In a recent Korean epidemiologic study, the overall CPP incidence was 122.8 per 100,000 children, with CPP incidence being greater in girls (262.8) than in boys (7.0). In Western countries, the estimated CPP prevalence is approximately 1 in 5,000 to 10,000 [13,24,25].

GENETIC ETIOLOGIES OF CPP

KISS1 and *KISS1R*

Gain-of-function mutations in the genes encoding kisspeptin and its receptor, *KISS1* and *KISS1R* (previously G protein coupled receptor 54 [*GPR54*]) have been suggested as causes of CPP (Table 1) [26,27]. First, loss-of-function mutations in the *KISS1R* gene could lead to idiopathic hypogonadotropic hypogonadism in 2003 [28,29]. Since 2003, further *KISS1R* mutations have been reported to cause idiopathic hypogonadotropic hypogonadism [30-32]. The first case of CPP with an identifiable *KISS1R* mutation was reported in 2008 [27]. A Brazilian girl exhibited breast development shortly after birth, with progression. At age 8, she had reached Tanner stage IV breast development, accelerated growth, and advanced bone age. A heterozygous gain-of-function mutation (p.Arg386Pro) in *KISS1R* was detected. Familial evaluation was not performed because the patient was adopted. In functional analysis, this mutation resulted in prolonged activation of intracellular *KISS1R* downstream signaling in response to kisspeptin stimulation.

Two years after reports of *KISS1R* gene mutations in a patient with CPP, gain-of-function mutations in the *KISS1* gene were discovered in three Brazilian children [33]. The boy with the *KISS1* gene mutation (p.Pro74Ser) exhibited secondary sexual development as early as 17 months of age. This mutation was inherited from his unaffected mother and grandmother. *In vitro*, the heterozygous mutant (p.Pro74Ser) was shown to decrease degradation, so this mutant may sustain increased protein bioavailability. Additionally, a homozygous mutation in the *KISS1* gene (p.His90Asp) in two unrelated girls with sporadic CPP was detected. This mutant was undetected in controls with normal pubertal progression. The affected girls exhibited breast development at 6 and 5.5 years of age. However, the p.His90Asp variant did not show increased activity or resistance to degradation *in vitro*.

The important function of the *KISS1*/*KISS1R* system in the pubertal process makes it necessary to investigate the mutations and polymorphisms in the *KISS1* gene and their association with CPP as well as the *KISS1R* gene. However, only small groups have described mutations in *KISS1* and *KISS1R* [34,35]. In Korea, researchers attempted to identify mutations in *KISS1* and *KISS1R* in Korean girls with CPP; however, definitive mutations were not found [26,36,37]. To date, *KISS1* and *KISS1R* mutations are rare causes of monogenic CPP. Further replication studies are required to validate these findings.

Table 1. **Known pathogenic genes associated with central precocious puberty**

Gene	Location	Protein	Function	Type of mutation	Other information
KISS1	1q32	Kisspeptin	Binds to KISS1 receptor	Gain-of-function missense	
KISS1R	19p13.3	KISS1R	Increased GnRH pulsatility	Gain-of-function missense	
MKRN3	15q11-q13	MKRN3	Ubiquitinylation, cell signaling	Loss-of-function	
				Stop codon	
				Frameshift	
				Missense	
				Deletion	
DLK1	14q32	Delta-like homolog 1	Pituitary cell differentiation	Loss-of-function	Metabolic abnormalities (obesity, type 2 diabetes, hyperlipidemia)
				Deletion	
				Frameshift	

MKRN3, makorin ring finger protein 3; GnRH, gonadotropin-releasing hormone; *DLK1*, delta-like homolog 1.

MKRN3

With the advancements in genetic evaluation techniques, such as next-generation sequencing, the genetics of CPP has been extensively investigated. In 2003, Abreu et al. [38] reported that makorin ring finger protein 3 (*MKRN3*) was detected in familial CPP through whole exome sequencing. Several variants predicted to be deleterious, such as frameshift, nonsense, and missense mutations in *MKRN3*, were found in five unrelated families. Since the initial report in 2013, *MKRN3* gene mutations have been reported in various ethnicities and countries [39,40]. *MKRN3* mutations are now the most commonly known genetic factors in CPP. In a recent review, 115 patients with CPP carrying *MKRN3* mutations were reported to harbor 48 different genetic variants [39]. The prevalence of *MKRN3* mutations was 33% to 46% in familial and 0.4% to 3.8% in sporadic CPP [40]. Furthermore, the frequency of *MKRN3* mutations appears to be higher among boys than among girls with CPP [41].

In Korea, Lee et al. [42] investigated *MKRN3* gene variants in 260 Korean girls with CPP. In this study, only one novel nonsense mutation (p.Gln281*) was detected in 260 girls with idiopathic CPP. The proband revealed a heterozygous C>T nucleotide change (c.841C>T), which predicted a truncated protein due to a premature stop codon in the MKRN3 gene. In this girl, basal and peak stimulated LH levels were relatively high, and there was no CNS abnormality. Her father could not recall the exact onset age of puberty, he just remembered that she was more mature than her peers. Her brother had the same nonsense mutation and advanced bone age. Thus, according to past history and clinical findings, her father and brother might have undergone precocious puberty, although exact pubertal onset is unknown. The *MKRN3* mutation was identified in only one out of 260 with CPP in Korea, which is significantly lower compared to Western countries that reported CPP to be associated with *MKRN3* gene mutations. These findings highlight the existence of genetic heterogeneity across ethnic groups and the need for further studies.

Genotype–phenotype correlation studies have reported that patients harboring *MKRN3* mutations appear to be similar to CPP patients without *MKRN3* mutations [40,43]. In 71 patients harboring *MKRN3* mutations, the average age at which secondary sexual characteristics appeared was 6.2 ± 1.2 years in girls and 7.1 ± 1.5 years in boys [43]. Interestingly, subjects with severe *MKRN3* mutations, including stop codon and frameshift, had more advanced bone age than subjects with missense mutations (2.3 ± 1.6 years vs. 1.6 ± 1.4 years). In addition, *MRKN3* mutations do not cause additional clinical phenotypes, such as obesity, except for early pubertal onset.

MKRN3 is a maternally imprinted gene; therefore, only the paternal allele is expressed. The exact mechanisms by which *MKRN3* mutations affect HPG axis activation remain unclear. The *MKRN3* gene was detected on chromosome 15q11.2, which is a critical region and has been shown to play a role in Prader–Willi syndrome (PWS) [44]. Delayed and incomplete puberty has been documented in most PWS patients; therefore, *MKRN3* deletion may not necessarily be the cause [45]. Interestingly, there have been a few reports on CPP in PWS patients [46,47]. *MKRN3* consists of three zinc finger domains (C3H), one zinc RING finger domain (C3HC4), and one MKRN3-specific Cys-His domain (CH), and is expressed ubiquitously in the human hypothalamus [48]. Based on its structure, *MKRN3* is predicted to function as a putative E3-ubiquitin ligase, and potentially affects gene expression, targeted protein degradation, and protein function modulation via its E3 ligase activity [39]. It can be assumed that the *MKRN3* gene has an inhibitory effect on pubertal onset. In Denmark, serum MKRN3 concentrations decreased before pubertal onset, and circulating *MKRN3* levels were negatively correlated with LH and FSH levels in healthy girls [49]. These findings support the hypothesis that the *MKRN3* gene may have an inhibitory effect on reproductive endocrine activity.

DLK1

In 2017, Dauber et al. [50] performed whole genome sequencing in a Brazilian family with five CPP females, and found a paternally inherited large deletion of the delta-like homolog 1 (*DLK1*) gene. A complex defect *DLK1* gene, approximately 14 kb heterozygous deletion in the first exon, including the translational start site, and a 269-base pair duplication of intron 3 was identified. Four affected sisters were described with the onset of secondary sexual development between the ages of 4.6 and 5.9 years. Similar to *MKRN3* gene inheritance, *DLK1* is a maternally imprinted, paternally expressed gene [51]. Recently, Gomes et al. [52] investigated 60 female patients with a history of CPP or early menarche for *DLK1* mutations. Three frameshift mutations with paternal expression in five female patients from three unrelated families were identified. Interestingly, patients harboring *DLK1* mutations observed more metabolic abnormalities, including glucose intolerance, type 2 diabetes mellitus, and obesity than CPP patients not harboring *DLK1* mutations [52]. Moreover, a rare heterozygous deletion in the splice site junction of *DLK1*

was identified in a Spanish girl with sporadic CPP. Her pubertal signs first began at the age of 5.7 [53].

Lee et al. [54] performed a genetic association study among Korean girls with CPP. The authors identified five polymorphisms via Sanger sequencing of *DLK1*. However, no high-impact mutations, such as frameshift or nonsense variants, were identified. In addition, Chen et al. [55] reported that no pathogenic *DLK1* mutations were identified in 19 Chinese girls with CPP and early puberty. Therefore, *DLK1* mutations may not be a frequent cause of CPP.

DLK1 is a noncanonical ligand that binds to the Notch receptors [56]. The Delta-Notch signaling pathway is highly conserved in all species, and *DLK1* is expressed in the normal pituitary gland and hypothalamus [56-58]. Further studies are needed to elucidate the reproductive function of *DLK1*.

In addition, both *MKRN3* and *DLK1* are imprinted genes. Imprinted genes whose expression is restricted to a single parental allele are important for growth and development. Therefore, imprinting disturbances due to epigenetics have been reported in several human disorders including PWS, Beckwith–Wiedemann syndrome, and Russell-Silver syndrome [59]. The mechanism by which imprinting genes influences pubertal expression remains unknown. Kotler and Haig [60] suggested that maternally expressed imprinted genes favor fast childhood development, while paternally expressed genes tend to delay growth. Also, patients with Temple syndrome show clearly CPP with accelerated bone age. Temple syndrome is the result of uniparental maternal expression of genes in chromosome 14 [61]. These findings provide a new perspective on the development of puberty.

OTHER CANDIDATE GENES

In the past decade, genetic loci that affect pubertal timing in normal girls have been identified using genome-wide association studies (GWASs) [62]. The majority of GWASs have used recalled age at menarche as it is the most frequent initial clinical hallmark of female pubertal onset. Several genes or loci, including lin-28 homolog B (*LIN28B*), tachykinin receptor 3 (*TACR3*), estrogen receptor 1 (*ESR1*), and 9q31.2, were associated with age at menarche in such GWASs [63-65]. Moreover, genes biologically linked to gonadotropin signaling, such as *GNRH1*, LH receptor, and FSH receptor, or encoding steroidogenesis enzymes, including *CYP19A1* and *CYP17*, may affect pubertal onset and progression; however, these pathogenic mutations have not been revealed in patients with CPP [66-69].

CONCLUSION

The regulation of puberty is multifactorial and is known to be associated with various genetic and environmental factors. However, the pathophysiology of pubertal onset is not entirely understood yet. Many research groups have sought to identify the genetic causes of CPP; but, to date, only four monogenic genes have been identified: *KISS1*, *KISS1R*, *MKRN3*, and *DLK1*. Moreover, mutation prevalence in *MKRN3* or *DLK1* in CPP varies considerably depending on ethnicity [42,70]. These findings suggest the existence of genetic heterogeneity across ethnic groups and highlight the requirement for further genetic studies.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTIONS

Conception or design: HSL.
Acquisition, analysis, or interpretation of data: HSL.
Drafting the work or revising: HSL.
Final approval of the manuscript: HSL.

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