Precis Future Med > Volume 7(4); 2023 > Article

Review Article
Precision and Future Medicine 2023; 7(4): 137-146.
Published online: December 27, 2023
DOI: https://doi.org/10.23838/pfm.2023.00156

# Genetic and epigenetic aspects of the *KISS1* and *KISS1R* genes in pubertal development and central precocious puberty: A review

Ahreum Kwon[1,2]

[1]Division of Pediatric Endocrinology, Severance Children's Hospital, Yonsei University College of Medicine, Seoul, Korea
[2]Department of Pediatrics, Endocrine Research Institute, Yonsei University College of Medicine, Seoul, Korea

Corresponding author: Ahreum Kwon Department of Pediatrics, Severance Children's Hospital, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea Tel: +82-2-2228-8203 E-mail: armea@yuhs.ac

Received November 20, 2023 Revised December 10, 2023 Accepted December 13, 2023



## Abstract

Go to :

The onset of puberty is a pivotal developmental milestone, and the release of gonadotropin-releasing hormone (GnRH) and luteinizing hormone is a key factor in the initiation of puberty. Both kisspeptin and its receptor (KISS1) and KISS1 receptor (KISS1R) play significant roles in regulating GnRH release, and consequently, the initiation of puberty. Central precocious puberty (CPP) is a condition in which the development of puberty is driven by the premature activation of the hypothalamic-pituitary-gonadal axis. In girls, CPP is primarily idiopathic, and genetic and epigenetic aspects of *KISS1* and *KISS1R* have been implicated in its etiology. This review aimed to provide an overview of the current knowledge regarding mutations and polymorphisms in *KISS1* and *KISS1R* associated with CPP. Additionally, this study provides a comprehensive review of the epigenetic regulation of the *KISS1* gene in the context of puberty onset and CPP.

**Keywords**: Epigenesis; KISS1; KISS1R; Precocious puberty

## INTRODUCTION

Go to :

Puberty is a biological maturation process that signifies the physical, hormonal, and psychological shifts from childhood to adulthood, culminating in the development of secondary sexual characteristics and the attainment of reproductive capability [1]. Precocious puberty is delineated by the initiation of puberty occurring 2 to 2.5 standard deviations ahead of the mean, and is defined as the manifestation of secondary sexual characteristics, such as breast development before the age of 8 in girls and testicular enlargement before the age of 9 in boys [2-4]. The precocious puberty can be categorized as central precocious puberty (CPP) and peripheral precocious puberty. The CPP occurs because of the premature reactivation of pulsatile hypothalamic gonadotropin-releasing hormone (GnRH) secretion, while peripheral precocious puberty is caused by excessive sex hormone secretion originates from a tumor or exogenous source independent of gonadotropin secretion and benign pubertal variants [5-7]. CPP accounts for 80% of precocious puberty cases [8], and the measurement of serum gonadotropins is essential. To exclude CPP, basal luteinizing hormone (LH) levels are utilized, with thresholds ranging from 0.1 to 1 IU/L being used variably [1]. Moreover, to confirm the activation of the hypothalamic-pituitary-gonadal (HPG) axis during puberty and diagnose CPP more accurately, the GnRH stimulation test is recognized as a definitive method [9]. For a more concise diagnostic approach, the use of a single LH measurement taken within 30 minutes of GnRH stimulation testing [10] or a single random measurement of urinary gonadotropin concentration has been suggested [11]. The standard treatment for CPP involves the use of long-acting GnRH agonists. The mechanism of action of GnRH agonists depends on the maintenance of elevated GnRH levels, which paradoxically leads to the downregulation and subsequent suppression of the HPG axis, thereby inhibiting gonadotropin secretion [12-14]. Various preparations are available, including intramuscular depots administered every 4 weeks,

12 weeks, or 6 months; subcutaneous injections administered every 6 months; and subcutaneous implants [15,16]. Diverse GnRH agonist preparations have been demonstrated to effectively suppress pubertal hormones and arrest or cause the regression of pubertal advancement [17-19].

CPP etiologies can be broadly categorized into two groups: those associated with central nervous system (CNS) lesions and those without CNS lesions. In cases with CNS lesions, the causes can include tumors such as hypothalamic hamartomas, congenital malformations like arachnoid cysts or hydrocephalus, and acquired lesions such as encephalitis or radiation exposure [1,6,20-22]. However, cases without CNS lesions are more common. CPP can also be secondary to chronic exposure to sex steroid hormones or endocrine disruptors [1,6]. Moreover, though still contentious, air pollution is also being considered a potential cause of precocious puberty [23]. The nutritional status and elevated serum leptin levels in overweight are believed to contribute, at least in part, to the earlier onset of puberty in overweight children [24]. While environmental and nutritional influences play a role in the development of CPP, it's equally crucial to consider the underlying genetic factors that might predispose certain individuals to this condition [6]. This is supported by the fact that CPP occurs approximately five to 15 times more frequently in girls than in boys, suggesting that genetic differences between males and females play a significant role in the occurrence of CPP [6,14]. In addition, syndromic CPP combined with multiple anomalies, such as Temple syndrome, Xp11.23–p.11.22 duplication syndrome, and Williams-Beuren syndrome, also suggests a genetic etiology [2,6]. The fact that approximately one-third of idiopathic central precocious puberty (ICPP) cases are familial CPP also implies the significance of genetic factors in CPP occurrence [25].

The elucidation of neuromodulators such as kisspeptin has contributed to the comprehension of pubertal developmental processes [26]. Mutations in makorin ring finger protein 3 (*MKRN3*) and delta like non-canonical Notch ligand 1 (*DLK1*) have been identified in individuals with familial CPP over the past decade [27]. These findings highlight the significant role of genetic factors in the underlying pathophysiology of CPP and stimulate ongoing research on the connections between genes associated with puberty and CPP. However, distinct variations in the timing of puberty are evident, even among genetically identical individuals [28], and research findings indicating the association of imprinted regions with menarche [29] suggest that genetic factors as well as epigenetic mechanisms influence the occurrence of CPP.

Understanding the genetic causes of CPP has had a significant impact, enabling more accurate and earlier diagnosis, facilitating familial counseling, and establishing potential avenues for future treatment targets. This review provides a comprehensive exploration of the three representative genetic causes of CPP and epigenetic dysregulation that contributes to CPP.

## GAIN-OF-FUNCTION MUTATIONS IN *KISS1* AND *KISS1R*

Go to :

The kisspeptin system is primarily made up of the kisspeptin and its receptor (KISS1) gene, which encodes the neuropeptide kisspeptin, and its specific receptor, KISS1R, found on GnRH neurons [30,31]. KISS1 and KISS1R are widely distributed, with notable expression levels in various organs, including the placenta, ovaries, and specific regions of the hypothalamus, such as the arcuate nucleus (ARC) and anteroventral periventricular nucleus/periventricular nucleus continuum (AVPV) [32,33]. The discovery of *KISS1R* loss-of-function mutations and rare inactivation *KISS1* mutations in patients with congenital hypogonadotropic hypogonadism emphasizes the significance of the kisspeptin system in human puberty and reproduction [30,31,34]. In addition, an elevation in serum kisspeptin levels has been observed in patients with CPP [35,36]. Moreover, the administration of kisspeptin triggers LH release in healthy individuals [37,38], whereas the LH increase following kisspeptin administration is diminished in men with congenital hypogonadotropic hypogonadism despite the preserved LH response to GnRH [39]. This suggests that the kisspeptin system is a critical regulator preceding GnRH release [40,41]. Specifically, kisspeptin neurons in the ARC contribute to pulsatile GnRH and LH

secretion [42,43], whereas those in the AVPV/periventricular nucleus continuum participate in the positive feedback of sex steroids, ultimately triggering a pre-ovulatory LH surge [43,44].

The significant role of the kisspeptin system in GnRH regulation and the discovery of loss-of-function mutations in *KISS1* and *KISS1R* associated with congenital hypogonadotropic hypogonadism suggest, conversely, that gain-of-function mutations could lead to the onset of precocious puberty. Nevertheless, only two rare mutations have been reported in *KISS1* and one in *KISS1R* in individuals with CPP. Two novel *KISS1* missense mutations, p.P74S and p.H90D, have been identified in patients with ICPP. Among them, the p.P74S variant exhibited increased resistance of kisspeptin to degradation compared to the wild-type, suggesting that this mutation could be a contributing factor to the development of precocious puberty [45]. In addition, an activating heterozygous mutation in *KISS1R* (p.R386P) was discovered in patients with CPP [46]. The p.R386P mutation induces prolonged activation of intracellular signaling pathways through kisspeptin owing to reduced degradation and internalization of KISS1R [46,47]. However, all three mutations are currently classified as either likely benign or variants of uncertain significance, according to the 2015 American College of Medical Genetics and Genomics Association for Molecular Pathology guidelines [48]. Therefore, the association between *KISS1* and *KISS1R* gain-of-function mutations and CPP is still not well established. Further reinforcement in the form of additional patient data or results from functional studies is necessary to elucidate the association between these mutations and CPP.

## SINGLE NUCLEOTIDE POLYMORPHISMS ASSOCIATED WITH CPP IN *KISS1* AND *KISS1R*

Go to :

Several single nucleotide polymorphisms (SNPs) in *KISS1 and KISS1R* are associated with CPP (Table 1) [49-55]. The 54650055 *G/T* polymorphism (p.P110T, rs192636495) [49,50] and the 55648176 *T/G* polymorphism [51] in the *KISS1* are suggested to have a protective effect against CPP. In addition, the haplotype *GGGC-ACCC*, comprising the *G* allele of SNP 55648176 *T/G* and the wild-type alleles of SNP 55648184 and SNP 55648186, along with the *GGA* haplotype, consisting of all the wild-type alleles of rs1132506 *G/C*, rs4889 *G/C*, and rs5780218 *A/-*, are suggested to have a protective effect against CPP [51,52]. On the contrary, three SNPs (rs1132506, rs35128240, and rs5780218) in the untranslated region of *KISS1* have been linked to an increased risk of CPP [51,52].

**Table 1.**

SNPs in *KISS1* and *KISS1R* found to have association with CPP

| Gene | Polymorphism position | dbSNP ID | Location | Major/Minor allele | Expression | Allele frequency | | Risk of CPP | Reference |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Case | Control | | |
| KISS1 | 54650055 | rs192636495 | Exon 3 | G/T | p.P110T | G: 0.961[a] T: 0.039[a] | G: 0.931[a] T: 0.069[a] | Protect | [49] |
| | | | | | | G: 0.970 T: 0.030 | G:0.922 T: 0.078 | Protect | [50] |
| | 55648176 | - | Exon 3 | T/G | - | T: 0.979 G: 0.021 | T: 0.941 G: 0.059 | Protect | [51] |
| | 55648184 | rs1132506 | Exon 3 3′ UTR | C/G | - | C: 0.448 G: 0.552 | C: 0.559 G: 0.441 | Increase | [51] |
| | | | | | | C: 0.573[b] G: 0.427[b] | C: 0.624 G: 0.376 | Increase | [52] |
| | 55648186 | rs35128240 | Exon 3 3′ UTR | -/T | - | -: 0.476 T: 0.524 | -: 0.569 T: 0.431 | Increase | [51] |
| | 204196482 | rs5780218 | 5′ UTR | A/- | - | A: 0.466[b] -: 0.534[b] | A: 0.539 -: 0.461 | Increase | [52] |
| KISS1R | 855765 | - | Promoter region 5′ UTR | A/G | | A: 0.963 G: 0.037 | A: 0.984 G: 0.016 | Increase | [53] |

| Gene | Polymorphism position | dbSNP ID | Location | Major/Minor allele | Expression | Allele frequency | | Risk of CPP | Reference |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Case | Control | | |
| | c.738+64 | rs350131 | Intron 4 | G/T | | G: 0.456<br>T: 0.544 | G: 0.359<br>T: 0.641 | Increase[c)] | [54] |
| | c.1091 | rs350132 | Exon 5 | T/A | p.L364H | T: 0.307<br>A: 0.693 | T: 0.222<br>A: 0.778 | Increase[c)] | [54] |

SNP, single nucleotide polymorphism; KISS1, kisspeptin and its receptor; KISS1R, KISS1 receptor; CPP, central precocious puberty; G, guanine; T, thymine; C, cytosine; UTR, untranslated region; A, adenine.

[a)] Allel frequency among Chinese subjects only;

[b)] The participants included individuals with CPP and early puberty;

[c)] The authors reported an increased risk of CPP; however, the allele frequency results are contradictory. The table presents the data reported in this study.

Download Table

Several SNPs have been reported in the *KISS1R* as well, but to date, only three have been reported to be associated with the risk of CPP (Table 1) [53,54]. Among them, rs350131 *G*> *T* and rs350132 *T*>*A* have been reported to increase the risk of CPP [54]; however, the allele frequency reported in the study showed that the minor allele frequency was lower in patients with CPP compared than in controls [54]. Considering that minor SNPs have also been reported in other studies among patients with CPP [55,56], reanalysis of the effect of this polymorphism on CPP is necessary.

## EPIGENETIC MECHANISMS OF THE *KISS1* GENE IN PUBERTAL DEVELOPMENT AND PRECOCIOUS PUBERTY

### Mechanisms of epigenetic control

Epigenetic modifications, which entail alterations in gene expression without modifying the DNA sequence, are widely acknowledged for their crucial role in the proper development and differentiation of various cell lineages within an organism. Presently, three acknowledged epigenetic mechanisms include: (1) chemical changes in DNA through DNA methylation and hydroxymethylation; (2) alterations in chromatin structure via post-translational modifications (PTMs) of histones, the protein components of nucleosomes; and (3) provision of epigenetic information by noncoding RNAs (ncRNAs), which can be microRNAs (miRNAs) or long intergenic noncoding RNAs (lincRNAs) [57].

Primary epigenetic modification of DNA involves the addition of a methyl group to cytosine residues, specifically at 5′-cytosine-phosphate-guanine-3′ (CpG) dinucleotide sequences [58,59]. DNA methylation is performed by DNA methyltransferases (DNMTs) and leads to 5-methylcytosine (5-mC) formation. Conversely, enzymes from the ten-eleven translocation (TET) family oxidize 5-mC to 5-hydroxymethylcytosine (5-hmC) [60,61]. Generally, increased levels of 5-mC are associated with transcriptional repression, whereas hypomethylation, characterized by reduced 5-mC and 5-hmC, is linked to the activation of gene transcription [62,63]. Both 5-mC and 5-hmC coexist throughout the genome. The 5-mC is more prevalent in silenced genes and in compacted chromosomal regions associated with heterochromatin (closed or condensed chromatin). In contrast, 5-hmC is found in more accessible regions or euchromatin (open or exposed chromatin), and is enriched in the promoter and enhancer regions of active genes [62].

Secondly, histones undergo various PTMs to reshape their chromatin structure, primarily on the N-terminal tails of core histones (H2A, H2B, H3, and H4) [64,65]. These tails are the most accessible regions for PTMs, including acetylation, methylation, phosphorylation, ubiquitination, and sumoylation [64]. Acetylation and methylation of lysine residues on histone tails are the most common PTMs and exhibit distinct patterns in heterochromatin and euchromatin [66]. Generally, acetylation by histone acetyltransferase enzymes (HATs) activates gene transcription, while deacetylation by histone deacetylases (HDACs) represses it [64,67,68]. Acetylation reduces the positive charge of lysine residues, weakening–histone interactions, and

allows easier access to the transcription machinery [67]. In contrast, histone methylation can either activate or repress transcription depending on the specific lysine residue and degree of methylation [66]. In particular, the polycomb group (PcG) and trithorax group (TrxG) are associated with alterations in chromatin structure through PTMs of histones and are pivotal regulators of numerous developmental genes. They operate in an antagonistic manner: PcG proteins induce repression by introducing repressor marks, such as H3K27Me3 and H2AK119Ub, whereas TrxG proteins activate gene expression by depositing activating marks, such as H3K4Me, H3K4Me2, and H3K4Me3, in the regulatory regions of genes [69,70].

ncRNAs also play a role in modulating epigenetic mechanisms. Contrary to previous beliefs, recent research has revealed that most of the human genome is transcribed into ncRNAs rather than protein-encoding mRNAs [71,72]. These ncRNAs have diverse biological roles, including regulation of gene expression at the transcriptional, RNA processing, and translation levels [73]. They are broadly categorized into two groups: small RNAs (sRNAs), typically 20 to 30 nucleotides long, and long noncoding RNAs (lncRNAs), which exceed 200 nucleotides in length [72,74]. miRNAs, endo-small inhibitory RNAs (endo-siRNAs), and piwiRNAs (piRNAs) are involved in epigenetic silencing [71,74,75]. In contrast, lncRNAs make more complex epigenetic contributions. Although lincRNAs do not encode proteins, they undergo polyadenylation and often originate from gene-free (intergenic) regions within the genome, which are referred to as lincRNAs. LincRNAs interact with chromatin-modifying complexes, guiding them to genomic regions that control gene expression [72,76].

## Epigenetic mechanisms of the *KISS1* gene in pubertal development

During pubertal development, epigenetic regulation ensures coordinated gene expression within an organism both temporally and in specific tissues. This function makes epigenetics a fundamental mechanism for gene-specific gatekeeper functions and provides the flexibility required for temporary modification of gene expression [77]. Specifically, GnRH secretion at the onset of puberty is influenced by the epigenetic regulation of the *KISS1* gene. Puberty initiation is marked by the removal of the central inhibitory mechanism regulating GnRH release [78]. During the prepubertal and infantile periods, GnRH neuronal secretion is primarily controlled by transsynaptic inhibition. However, as soon as puberty begins, this inhibitory control relaxes, resulting in a simultaneous increase in excitatory inputs to the GnRH network [79]. The relaxation of inhibitory control and the concurrent increase in excitatory neurotransmission are now widely accepted as crucial opposing mechanisms that collectively initiate the pubertal process [80-83]. Ultimately, this leads to an increase in the release of GnRH, which marks the onset of puberty. Recent findings indicate that the intercellular balance between excitatory and inhibitory mechanisms is reflected at the genomic level [57]. This is evident from the emergence of three gene groups: puberty inhibitor genes, puberty-activating genes, and genes that exhibit dual effects depending on the hormonal environment and cellular identity [57]. Among these groups, the *KISS1* gene is included among the puberty-activating genes.

During the transition from the prepubertal period to puberty in the hypothalamus, *KISS1* expression is intricately regulated through a complex interplay of epigenetic modifications and enzymatic processes, orchestrating the shift from repression in the prepubertal phase to activation during puberty. Within the *KISS1* promoter is a bivalent region in which both repressive and activating marks coexist, enabling the promoter to be in a poised state of activation in response to various incoming signals [84]. During the prepubertal period, the *KISS1* gene is repressed by a series of epigenetic modifications in its promoter region. Specifically, CpG islands in the promoter region undergo methylation and a repressive histone mark, H3K27me3, is added. These modifications are catalyzed by PcG enzymes, specifically embryonic ectoderm development (EED) and chromobox protein homolog 7 (CBX7) [57,64,77]. In a study involving female rats, the presence of two critical PcG members, *Eed* and *Cbx7*, within ARC kisspeptin neurons and their protein products were observed to interact with the *Kiss1* promoter during prepubertal development [77]. Transcriptional repressors of the PcG prevent early onset of puberty by suppressing *KISS1* transcription in kisspeptin, neurokinin B, and

dynorphin (KNDy) neurons located within the ARC [77]. Reinforcing the repressive effect on *KISS1*, the sirtuin type 1 (SIRT1) enzyme interacts with PcG proteins and removes histone acetylation [85]. Furthermore, *KISS1* expression undergoes additional repression through the action of enzymes such as GATA zinc finger domain containing 1 (GATAD1) and KDM1A, which function as histone demethylases. These enzymes have distinct roles: GATAD1 serves as a chromatin reader that recruits the histone eraser KDM1A [57,86]. *In vitro* studies demonstrated that KDM1A recruitment increases with the overexpression of GATAD1, leading to a significant reduction in the loss of activating H3K4me3/2 marks in the regulatory regions of the *KISS1* gene [87]. These findings support the notion that GATAD1 contributes to the attenuation of *KISS1* activity partly by facilitating the removal of the H3K4me2 mark from the promoter of the gene through the recruitment of KDM1A [57].

In contrast, to initiate the transition to puberty, *KISS1* undergoes changes in its regulatory regions, shifting from a repressed to an activated state. This transformation begins with the removal of the repressor enzymes, EED, CBX7, and SIRT1, from the *KISS1* promoter. As puberty nears completion, there is a simultaneous increase in methylation within the promoter regions of *Eed* and *Cbx7* in the ARC, along with a significant reduction in the expression of both genes, independent of estrogen influence [57,77]. Crucially, the removal of PcG components, EED and CBX7, from the promoter is accompanied by reorganization of the chromatin state, marked by increased levels of epigenetic modifications, such as H3K9ac, H3K14ac, and H3K4me3, which are associated with gene activation. This activation is likely mediated by members of the TrxG complex because of their well-established antagonistic activity against PcG [88]. Mixed lineage leukemia 1 (MLL1) and MLL3, two components of the TrxG complex, exert their transactivational influence on the promoter and enhancer regions of the *Kiss1* gene, respectively, during a period when the inhibitory effects of the PcG complex diminish [89]. Additionally, the TrxG member ubiquitously transcribed tetratricopeptide repeat, X chromosome (UTX) may aid in PcG removal by demethylating the repressive histone H3K27me3 mark, thereby allowing for an increase in H3K27ac, a characteristic feature of an active enhancer [89,90]. Additionally, other activating enzymes such as HAT and p300/CBP participate in this activation process, catalyzing the addition of acetylations, such as H3K9ac, H3K14ac, and H3K27ac, in both the promoter and enhancer regions of *KISS1* to promote its expression [57,77]. Furthermore, *KISS1* mRNA expression increased, whereas GATAD1 expression decreased in the medial basal hypothalamus (MBH) of ovary-intact females during the transition from juvenile to puberty. The decline in the association of GATAD1 and KDM1A with *KISS1* promoters, along with the simultaneous increase in H3K4me2 levels observed in monkey MBH at the onset of puberty, strongly supports the presence of an epigenetic repression mechanism that is alleviated during the re-establishment of GnRH pulsatility during the transition from infancy to juvenility in monkeys [57]. Consequently, in line with these crucial histone PTMs, the epigenetic regulation of *Kiss1* shifts from a repressive to an active state around the time of puberty, and there is an upregulation of *Kiss1* mRNA expression in the ARC [57,77].

The regulatory response of kisspeptin neurons to estradiol (E2) differs depending on their location, with distinct reactions observed in the ARC versus the AVPV. E2 inhibits *Kiss1* expression in ARC KNDy neurons, but enhances it in AVPV kisspeptin neurons; however, the specific mechanisms underlying this difference remain unknown. In AVPV, E2 plays an epigenetic role by promoting the acetylation of H3 in the *Kiss1* promoter region, leading to its increased expression [91]. E2 also induces estradiol receptor alpha (ERα) binding to the *Kiss1* promoter exclusively in the AVPV. Conversely, H3 acetylation is reduced in the ARC, resulting in decreased *Kiss1* expression [91]. Furthermore, an estrogen-responsive enhancer region in the intergenic 3′ region of the *Kiss1* gene was identified in AVPV kisspeptin neurons but not in ARC [91]. Therefore, these findings have unveiled an epigenetic role in E2 positive feedback within the AVPV; however, it is still unclear whether a similar epigenetic mechanism is involved in the inhibitory effect of estrogen on ARC *Kiss1* expression.

### Epigenetic mechanisms of the *KISS1* gene in precocious puberty

Despite numerous studies indicating the importance of the kisspeptin system in pubertal development and the initiation of puberty, which depends on the epigenetic control of the *KISS1* gene's repression or expression, there is still insufficient research on the association between precocious puberty and the epigenetic mechanisms of *KISS1*. Current research has predominantly focused on correlations with delayed puberty or hypogonadism. For instance, downregulation of Mll1 expression in the ARC using siRNA results in inhibited *Kiss1* expression, thereby delaying puberty [89], and clustered regularly interspaced short palindromic repeats-associated protein 9 (CRISPR-Cas9) system epigenetic remodeling approach that hinders Mll3 action on the *Kiss1* enhancer region also postpones the peripubertal increase in *Kiss1* expression and the onset of puberty [89]. Additionally, inactive mutations in chromodomain helicase DNA binding protein 7 (CHD7), which normally antagonizes PcG activity by binding to activating marks H3K4me2/me3 via its chromodomain, lead to hypothalamic hypogonadism in humans, suggesting a translational perspective on the role of TrxG in puberty control [92]. Furthermore, GATAD1 overexpression in the ARC of immature rats significantly delays the onset of puberty and disrupts estrous cyclicity [93]. On the contrary, it has been observed that the elimination of EED and SIRT1 repressor enzymes from the *KISS1* promoter to initiate puberty can be accelerated depending on nutritional status, potentially causing either precocious puberty or delayed puberty [77].

## CONCLUSION

Go to :

The genetic basis of CPP has been widely discussed, with particular emphasis on the kisspeptin system because of its central role in pubertal onset. Studies have examined multiple genetic mutations and polymorphisms in *KISS1* and *KISS1R*, some of which have been correlated with CPP. Additionally, given the importance of epigenetic regulation in determining the onset of puberty through the expression/repression of the *KISS1* gene, active research on the epigenetic alterations of the *KISS1* gene and its relationship with puberty onset is ongoing. However, studies on the epigenetic alteration of the *KISS1* gene as a cause of CPP remain limited. Instead, epigenetic alterations have been identified in other genes such as *MKRN3, DLK1*, tachykinin precursor 3 (*TAC3*), *GNRH*, and more. It is crucial to consider the epigenetic regulation of various genes related to pubertal onset as a potential cause of CPP. Understanding the genetic causes of CPP has significant implications, allowing for a more precise and earlier diagnosis, supporting familial counseling, and paving the way for potential future treatment targets.

## CONFLICTS OF INTEREST

Go to :

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

## Notes

Go to :

### AUTHOR CONTRIBUTIONS

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

## REFERENCES

Go to :

1. Cheuiche AV, da Silveira LG, de Paula LC, Lucena IR, Silveiro SP. Diagnosis and management of precocious sexual maturation: an updated review. Eur J Pediatr 2021;180:3073–87.
Article PubMed PDF

2. Brito VN, Canton AP, Seraphim CE, Abreu AP, Macedo DB, Mendonca BB, et al. The congenital and acquired mechanisms implicated in the etiology of central precocious puberty. Endocr Rev 2023;44:193–221.
Article PubMed PMC PDF

3. Marshall WA, Tanner JM. Variations in pattern of pubertal changes in girls. Arch Dis Child 1969;44:291–303.
Article PubMed PMC

4. Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in boys. Arch Dis Child 1970;45:13–23.
Article PubMed PMC

5. Cantas-Orsdemir S, Eugster EA. Update on central precocious puberty: from etiologies to outcomes. Expert Rev Endocrinol Metab 2019;14:123–30.
Article PubMed

6. Latronico AC, Brito VN, Carel JC. Causes, diagnosis, and treatment of central precocious puberty. Lancet Diabetes Endocrinol 2016;4:265–74.
Article PubMed

7. Brito VN, Spinola-Castro AM, Kochi C, Kopacek C, Silva PC, Guerra-Junior G. Central precocious puberty: revisiting the diagnosis and therapeutic management. Arch Endocrinol Metab 2016;60:163–72.
Article PubMed

8. Parent AS, Teilmann G, Juul A, Skakkebaek NE, Toppari J, Bourguignon JP. The timing of normal puberty and the age limits of sexual precocity: variations around the world, secular trends, and changes after migration. Endocr Rev 2003;24:668–93.
Article PubMed

9. Carel JC, Leger J. Clinical practice: precocious puberty. N Engl J Med 2008;358:2366–77.
Article PubMed

10. Houk CP, Kunselman AR, Lee PA. The diagnostic value of a brief GnRH analogue stimulation test in girls with central precocious puberty: a single 30-minute post-stimulation LH sample is adequate. J Pediatr Endocrinol Metab 2008;21:1113–8.
Article PubMed

11. Lee SY, Kim JM, Kim YM, Lim HH. Single random measurement of urinary gonadotropin concentration for screening and monitoring girls with central precocious puberty. Ann Pediatr Endocrinol Metab 2021;26:178–84.
Article PubMed PMC PDF

12. Belchetz PE, Plant TM, Nakai Y, Keogh EJ, Knobil E. Hypophysial responses to continuous and intermittent delivery of hypopthalamic gonadotropin-releasing hormone. Science 1978;202:631–3.
Article PubMed

13. Mul D, Hughes IA. The use of GnRH agonists in precocious puberty. Eur J Endocrinol 2008;159 Suppl 1:S3–8.
Article PubMed

14. Cho AY, Ko SY, Lee JH, Kim EY. Effects of gonadotropin-releasing hormone agonist treatment on final adult height in boys with idiopathic central precocious puberty. Ann Pediatr Endocrinol Metab 2021;26:259–65.
Article PubMed PMC PDF

15. Guaraldi F, Beccuti G, Gori D, Ghizzoni L. Management of endocrine disease: long-term outcomes of the treatment of central precocious puberty. Eur J Endocrinol 2016;174:R79–87.
Article PubMed

16. Eugster EA. Treatment of central precocious puberty. J Endocr Soc 2019;3:965–72.
Article PubMed PMC

17. Jeon MJ, Choe JW, Chung HR, Kim JH. Short-term efficacy of 1-month and 3-month gonadotropin-releasing hormone agonist depots in girls with central precocious puberty. Ann Pediatr Endocrinol Metab 2021;26:171–7.
Article PubMed PMC PDF

18. Klein KO, Freire A, Gryngarten MG, Kletter GB, Benson M, Miller BS, et al. Phase 3 trial of a small-volume subcutaneous 6-month duration leuprolide acetate treatment for central precocious puberty. J Clin Endocrinol Metab 2020;105:e3660. –71.
Article PubMed PMC PDF

19. Lewis KA, Goldyn AK, West KW, Eugster EA. A single histrelin implant is effective for 2 years for treatment of central precocious puberty. J Pediatr 2013;163:1214–6.
Article PubMed PMC

20. Huynh QT, Ho BT, Le NQ, Trinh TH, Lam LH, Nguyen NT, et al. Pathological brain lesions in girls with central precocious puberty at initial diagnosis in Southern Vietnam. Ann Pediatr Endocrinol Metab 2022;27:105–12.
Article PubMed PMC PDF

21. Bizzarri C, Bottaro G. Endocrine implications of neurofibromatosis 1 in childhood. Horm Res Paediatr 2015;83:232–41.
Article PubMed PDF

22. Harrison VS, Oatman O, Kerrigan JF. Hypothalamic hamartoma with epilepsy: review of endocrine comorbidity. Epilepsia 2017;58 Suppl 2:50–9.
Article PubMed PMC PDF

23. Heo YJ, Kim HS. Ambient air pollution and endocrinologic disorders in childhood. Ann Pediatr Endocrinol Metab 2021;26:158–70.
Article PubMed PMC PDF

24. Bianco SD. A potential mechanism for the sexual dimorphism in the onset of puberty and incidence of idiopathic central precocious puberty in children: sex-specific kisspeptin as an integrator of puberty signals. Front Endocrinol (Lausanne) 2012;3:149.
Article PubMed PMC

25. de Vries L, Kauschansky A, Shohat M, Phillip M. Familial central precocious puberty suggests autosomal dominant inheritance. J Clin Endocrinol Metab 2004;89:1794–800.
Article PubMed

26. Livadas S, Chrousos GP. Molecular and environmental mechanisms regulating puberty initiation: an integrated approach. Front Endocrinol (Lausanne) 2019;10:828.
Article PubMed PMC

27. Abreu AP, Dauber A, Macedo DB, Noel SD, Brito VN, Gill JC, et al. Central precocious puberty caused by mutations in the imprinted gene MKRN3. N Engl J Med 2013;368:2467–75.
Article PubMed PMC

28. Rzeczkowska PA, Hou H, Wilson MD, Palmert MR. Epigenetics: a new player in the regulation of mammalian puberty. Neuroendocrinology 2014;99:139–55.
Article PubMed PDF

29. Perry JR, Day F, Elks CE, Sulem P, Thompson DJ, Ferreira T, et al. Parent-of-origin-specific allelic associations among 106 genomic loci for age at menarche. Nature 2014;514:92–7.
PubMed PMC

30. Seminara SB, Messager S, Chatzidaki EE, Thresher RR, Acierno JS Jr, Shagoury JK, et al. The GPR54 gene as a regulator of puberty. N Engl J Med 2003;349:1614–27.
Article PubMed

31. de Roux N, Genin E, Carel JC, Matsuda F, Chaussain JL, Milgrom E. Hypogonadotropic hypogonadism due to loss of function of the KiSS1-derived peptide receptor GPR54. Proc Natl Acad Sci U S A 2003;100:10972–6.
Article PubMed PMC

32. Kwon A, Eom JY, Lee WJ, Choi HS, Song K, Suh J, et al. Serum kisspeptin levels mainly depend on ovarian expression of Kiss1 mRNA in female rats. Front Physiol 2022;13:998446.
Article PubMed PMC

33. Terao Y, Kumano S, Takatsu Y, Hattori M, Nishimura A, Ohtaki T, et al. Expression of KiSS-1, a metastasis suppressor gene, in trophoblast giant cells of the rat placenta. Biochim Biophys Acta 2004;1678:102–10.
Article PubMed

34. Topaloglu AK, Tello JA, Kotan LD, Ozbek MN, Yilmaz MB, Erdogan S, et al. Inactivating KISS1 mutation and hypogonadotropic hypogonadism. N Engl J Med 2012;366:629–35.
Article PubMed

35. Rhie YJ, Lee KH, Eun SH, Choi BM, Chae HW, Kwon AR, et al. Serum kisspeptin levels in Korean girls with central precocious puberty. J Korean Med Sci 2011;26:927–31.
Article PubMed PMC PDF

36. Xue J, Song W, Si M, Sun C, Li K, Wang W, et al. Serum kisspeptin and AMH levels are good references for precocious puberty progression. Int J Endocrinol 2020;2020:3126309.
Article PubMed PMC PDF

37. George JT, Veldhuis JD, Roseweir AK, Newton CL, Faccenda E, Millar RP, et al. Kisspeptin-10 is a potent stimulator of LH and increases pulse frequency in men. J Clin Endocrinol Metab 2011;96:E1228–36.
Article PubMed PMC

38. Chan YM, Butler JP, Sidhoum VF, Pinnell NE, Seminara SB. Kisspeptin administration to women: a window into endogenous kisspeptin secretion and GnRH responsiveness across the menstrual cycle. J Clin Endocrinol Metab 2012;97:E1458–67.
Article PubMed PMC

39. Abbara A, Eng PC, Phylactou M, Clarke SA, Mills E, Chia G, et al. Kisspeptin-54 accurately identifies hypothalamic gonadotropin-releasing hormone neuronal dysfunction in men with congenital hypogonadotropic hypogonadism. Neuroendocrinology 2021;111:1176–86.
Article PubMed PDF

40. Tena-Sempere M. The roles of kisspeptins and G proteincoupled receptor-54 in pubertal development. Curr Opin Pediatr 2006;18:442–7.
Article PubMed

41. Dhillo WS, Chaudhri OB, Patterson M, Thompson EL, Murphy KG, Badman MK, et al. Kisspeptin-54 stimulates the hypothalamic-pituitary gonadal axis in human males. J Clin Endocrinol Metab 2005;90:6609–15.
Article PubMed

42. Clarkson J, Han SY, Piet R, McLennan T, Kane GM, Ng J, et al. Definition of the hypothalamic GnRH pulse generator in mice. Proc Natl Acad Sci U S A 2017;114:E10216–23.
Article PubMed PMC

43. Wang L, Moenter SM. Differential roles of hypothalamic AVPV and arcuate kisspeptin neurons in estradiol feedback regulation of female reproduction. Neuroendocrinology 2020;110:172–84.
Article PubMed PMC PDF

44. Zhang C, Bosch MA, Qiu J, Ronnekleiv OK, Kelly MJ. 17β-Estradiol increases persistent Na(+) current and excitability of AVPV/PeN Kiss1 neurons in female mice. Mol Endocrinol 2015;29:518–27.
Article PubMed PMC PDF

45. Silveira LG, Noel SD, Silveira-Neto AP, Abreu AP, Brito VN, Santos MG, et al. Mutations of the KISS1 gene in disorders of puberty. J Clin Endocrinol Metab 2010;95:2276–80.
Article PubMed PMC PDF

46. Teles MG, Bianco SD, Brito VN, Trarbach EB, Kuohung W, Xu S, et al. A GPR54-activating mutation in a patient with central precocious puberty. N Engl J Med 2008;358:709–15.
Article PubMed PMC

47. Bianco SD, Vandepas L, Correa-Medina M, Gereben B, Mukherjee A, Kuohung W, et al. KISS1R intracellular trafficking and degradation: effect of the Arg386Pro diseaseassociated mutation. Endocrinology 2011;152:1616–26.
Article PubMed PMC PDF

48. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015;17:405–24.
Article PubMed PMC PDF

49. Luan X, Zhou Y, Wang W, Yu H, Li P, Gan X, et al. Association study of the polymorphisms in the KISS1 gene with central precocious puberty in Chinese girls. Eur J Endocrinol 2007;157:113–8.
Article PubMed

50. Ko JM, Lee HS, Hwang JS. KISS1 gene analysis in Korean girls with central precocious puberty: a polymorphism, p.P110T, suggested to exert a protective effect. Endocr J 2010;57:701–9.
Article PubMed

51. Rhie YJ, Lee KH, Ko JM, Lee WJ, Kim JH, Kim HS. KISS1 gene polymorphisms in Korean girls with central precocious puberty. J Korean Med Sci 2014;29:1120–5.
Article PubMed PMC PDF

52. Li D, Wu Y, Cheng J, Liu L, Li X, Chen D, et al. Association of polymorphisms in the kisspeptin/GPR54 pathway genes with risk of early puberty in Chinese girls. J Clin Endocrinol Metab 2020;105:dgz229.
Article PubMed PDF

53. Luan X, Yu H, Wei X, Zhou Y, Wang W, Li P, et al. GPR54 polymorphisms in Chinese girls with central precocious puberty. Neuroendocrinology 2007;86:77–83.
Article PubMed PDF

54. Oh YJ, Rhie YJ, Nam HK, Kim HR, Lee KH. Genetic variations of the KISS1R gene in Korean girls with central precocious puberty. J Korean Med Sci 2017;32:108–14.
Article PubMed PMC PDF

55. Ghaemi N, Ghahraman M, Noroozi Asl S, Vakili R, Fardi Golyan F, Moghbeli M, et al. Novel DNA variation of GPR54 gene in familial central precocious puberty. Ital J Pediatr 2019;45:10.
Article PubMed PMC PDF

56. Pagani S, Calcaterra V, Acquafredda G, Montalbano C, Bozzola E, Ferrara P, et al. MKRN3 and KISS1R mutations in precocious and early puberty. Ital J Pediatr 2020;46:39.
Article PubMed PMC PDF

57. Toro CA, Aylwin CF, Lomniczi A. Hypothalamic epigenetics driving female puberty. J Neuroendocrinol 2018;30:e12589.
Article PubMed PMC PDF

58. Jaenisch R, Bird A. Epigenetic regulation of gene expression: how the genome integrates intrinsic and environmental signals. Nat Genet 2003;33 Suppl:245–54.
Article PubMed PDF

59. Bjornsson HT, Fallin MD, Feinberg AP. An integrated epigenetic and genetic approach to common human disease. Trends Genet 2004;20:350–8.
Article PubMed

60. Tahiliani M, Koh KP, Shen Y, Pastor WA, Bandukwala H, Brudno Y, et al. Conversion of 5-methylcytosine to 5-hydroxymethylcytosine in mammalian DNA by MLL partner TET1. Science 2009;324:930–5.
Article PubMed PMC

61. Koh KP, Yabuuchi A, Rao S, Huang Y, Cunniff K, Nardone J, et al. Tet1 and Tet2 regulate 5-hydroxymethylcytosine production and cell lineage specification in mouse embryonic stem cells. Cell Stem Cell 2011;8:200–13.
Article PubMed PMC

62. Ficz G, Branco MR, Seisenberger S, Santos F, Krueger F, Hore TA, et al. Dynamic regulation of 5-hydroxymethylcytosine in mouse ES cells and during differentiation. Nature 2011;473:398–402.
Article PubMed PDF

63. Guo JU, Su Y, Zhong C, Ming GL, Song H. Emerging roles of TET proteins and 5-hydroxymethylcytosines in active DNA demethylation and beyond. Cell Cycle 2011;10:2662–8.
Article PubMed PMC

64. Kouzarides T. Chromatin modifications and their function. Cell 2007;128:693–705.
Article PubMed

65. Khorasanizadeh S. The nucleosome: from genomic organization to genomic regulation. Cell 2004;116:259–72.
Article PubMed

66. Jenuwein T, Allis CD. Translating the histone code. Science 2001;293:1074–80.
Article PubMed

67. Yun M, Wu J, Workman JL, Li B. Readers of histone modifications. Cell Res 2011;21:564–78.
Article PubMed PMC PDF

68. Ruthenburg AJ, Li H, Patel DJ, Allis CD. Multivalent engagement of chromatin modifications by linked binding modules. Nat Rev Mol Cell Biol 2007;8:983–94.
Article PubMed PMC PDF

69. Schuettengruber B, Chourrout D, Vervoort M, Leblanc B, Cavalli G. Genome regulation by polycomb and trithorax proteins. Cell 2007;128:735–45.
Article PubMed

70. Lomniczi A, Wright H, Ojeda SR. Epigenetic regulation of female puberty. Front Neuroendocrinol 2015;36:90–107.
Article PubMed PMC

71. Huang B, Jiang C, Zhang R. Epigenetics: the language of the cell? Epigenomics 2014;6:73–88.
Article PubMed

72. Batista PJ, Chang HY. Long noncoding RNAs: cellular address codes in development and disease. Cell 2013;152:1298–307.
Article PubMed PMC

73. Cech TR, Steitz JA. The noncoding RNA revolution-trashing old rules to forge new ones. Cell 2014;157:77–94.
Article PubMed

74. Filipowicz W, Bhattacharyya SN, Sonenberg N. Mechanisms of post-transcriptional regulation by microRNAs: are the answers in sight? Nat Rev Genet 2008;9:102–14.
Article PubMed PDF

75. Kim VN. Small RNAs just got bigger: piwi-interacting RNAs (piRNAs) in mammalian testes. Genes Dev 2006;20:1993–7.
Article PubMed

76. Spitale RC, Tsai MC, Chang HY. RNA templating the epigenome: long noncoding RNAs as molecular scaffolds. Epigenetics 2011;6:539–43.
Article PubMed PMC

77. Lomniczi A, Loche A, Castellano JM, Ronnekleiv OK, Bosch M, Kaidar G, et al. Epigenetic control of female puberty. Nat Neurosci 2013;16:281–9.
Article PubMed PMC PDF

78. Terasawa E, Bridson WE, Nass TE, Noonan JJ, Dierschke DJ. Developmental changes in the luteinizing hormone secretory pattern in peripubertal female rhesus monkeys: comparisons between gonadally intact and ovariectomized animals. Endocrinology 1984;115:2233–40.
Article PubMed

79. Ojeda SR. The mystery of mammalian puberty: how much more do we know? Perspect Biol Med 1991;34:365–83.
Article PubMed

80. Blank MS, Panerai AE, Friesen HG. Opioid peptides modulate luteinizing hormone secretion during sexual maturation. Science 1979;203:1129–31.
Article PubMed

81. Mahesh VB, Nazian SJ. Role of sex steroids in the initiation of puberty. J Steroid Biochem 1979;11(1B):587–91.
Article PubMed

82. Sirinathsinghji DJ, Motta M, Martini L. Induction of precocious puberty in the female rat after chronic naloxone administration during the neonatal period: the opiate 'brake' on prepubertal gonadotrophin secretion. J Endocrinol 1985;104:299–307.
Article PubMed

83. Bourguignon JP, Gerard A, Mathieu J, Mathieu A, Franchimont P. Maturation of the hypothalamic control of pulsatile gonadotropin-releasing hormone secretion at onset of puberty. I. Increased activation of N-methyl-D-aspartate receptors. Endocrinology 1990;127:873–81.
Article PubMed

84. Bernstein BE, Mikkelsen TS, Xie X, Kamal M, Huebert DJ, Cuff J, et al. A bivalent chromatin structure marks key developmental genes in embryonic stem cells. Cell 2006;125:315–26.
Article PubMed

85. Vazquez MJ, Toro CA, Castellano JM, Ruiz-Pino F, Roa J, Beiroa D, et al. SIRT1 mediates obesity- and nutrient-dependent perturbation of pubertal timing by epigenetically controlling Kiss1 expression. Nat Commun 2018;9:4194.
Article PubMed PMC PDF

86. Motti ML, Meccariello R. Minireview: the epigenetic modulation of KISS1 in reproduction and cancer. Int J Environ Res Public Health 2019;16:2607.
Article PubMed PMC

87. Shi Y, Lan F, Matson C, Mulligan P, Whetstine JR, Cole PA, et al. Histone demethylation mediated by the nuclear amine oxidase homolog LSD1. Cell 2004;119:941–53.
Article PubMed

88. Shilatifard A. The COMPASS family of histone H3K4 methylases: mechanisms of regulation in development and disease pathogenesis. Annu Rev Biochem 2012;81:65–95.
Article PubMed PMC

89. Toro CA, Wright H, Aylwin CF, Ojeda SR, Lomniczi A. Trithorax dependent changes in chromatin landscape at enhancer and promoter regions drive female puberty. Nat Commun 2018;9:57.
Article PubMed PMC PDF

90. Schuettengruber B, Martinez AM, Iovino N, Cavalli G. Trithorax group proteins: switching genes on and keeping them active. Nat Rev Mol Cell Biol 2011;12:799–814.
Article PubMed PDF

91. Tomikawa J, Uenoyama Y, Ozawa M, Fukanuma T, Takase K, Goto T, et al. Epigenetic regulation of Kiss1 gene expression mediating estrogen-positive feedback action in the mouse brain. Proc Natl Acad Sci U S A 2012;109:E1294–301.
Article PubMed PMC

92. Kim HG, Kurth I, Lan F, Meliciani I, Wenzel W, Eom SH, et al. Mutations in CHD7, encoding a chromatin-remodeling protein, cause idiopathic hypogonadotropic hypogonadism and Kallmann syndrome. Am J Hum Genet 2008;83:511–9.
Article PubMed PMC

93. Lomniczi A, Wright H, Castellano JM, Matagne V, Toro CA, Ramaswamy S, et al. Epigenetic regulation of puberty via Zinc finger protein-mediated transcriptional repression. Nat Commun 2015;6:10195.
Article PubMed PMC PDF