Genetic and Neuropeptide Aspects in Central Precocious Puberty (CPP)

Background: Central precocious puberty (CPP) is defined by the premature activation of the hypothalamic-pituitary-gonadal (HPG) axis, leading to early development of secondary sexual characteristics. CPP is more common in girls and can adversely affect growth and psychosocial outcomes.

Objective: This review synthesizes current evidence on the genetic and neuropeptidergic mechanisms underlying CPP, focusing on their diagnostic and therapeutic relevance.

Methods: A comprehensive analysis of recent literature was conducted, including genetic studies on imprinted genes such as MKRN3 and DLK1, rare mutations in KISS1 and KISS1R, and the role of neuropeptides, particularly kisspeptin and neurokinin B, in HPG axis regulation. Diagnostic approaches, including clinical evaluation, biochemical markers, pelvic ultrasound parameters, and genetic testing, are discussed. Therapeutic strategies with gonadotropin-releasing hormone analogs (GnRHa) and emerging neuropeptide modulators are reviewed.

Results: Genetic mutations in MKRN3 and DLK1 are recognized as major monogenic causes of familial CPP, while rare activating mutations in KISS1 and KISS1R confirm the essential role of kisspeptin signaling. Advances in pelvic ultrasound and hormonal assays have improved diagnostic accuracy, although overlap with benign variants remains a challenge. GnRHa therapy is the gold standard for halting pubertal progression and optimizing final adult height. However, long-term psychosocial and metabolic outcomes warrant further research.

Conclusions: Understanding the genetic and neuroendocrine basis of CPP enables earlier and more accurate diagnosis and paves the way for personalized treatment strategies. Future research should focus on refining biomarkers, developing alternative therapeutic options such as kisspeptin antagonists, and elucidating the long-term outcomes of treated individuals.

Keywords: Central precocious puberty, MKRN3, DLK1, Kisspeptin, Neurokinin B, Genetic testing, Gonadotropin-releasing hormone analogs, Pubertal timing.

Introduction.

Puberty is a complex neuroendocrine process marked by the reactivation of the hypothalamic-pituitary-gonadal (HPG) axis, ultimately leading to reproductive maturity. In girls, the hallmarks of pubertal onset include breast development, thelarche, accelerated growth, and menarche. However, when these secondary sexual characteristics appear before the age of 8, the condition is defined as precocious puberty (PP). This disorder is more common in girls and can result in compromised adult height, psychological stress, and potential long-term health risks if not managed effectively [1].

Central precocious puberty (CPP) is the gonadotropin-dependent form of PP and is caused by premature activation of the HPG axis. The condition involves elevated gonadotropin-releasing hormone (GnRH) secretion from the hypothalamus, leading to the secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which stimulate the ovaries to produce sex steroids [2, 3]. In contrast, peripheral precocious puberty (PPP) occurs independently of GnRH and is often caused by genetic syndromes or hormone-secreting tumours[1, 2].

Recent researches have illuminated the pivotal roles of genetic factors and neuropeptides in governing the timing of pubertal onset. A substantial

proportion of idiopathic CPP cases have been linked to mutations in genes such as MKRN3, DLK1, KISS1, and KISS1R, many of which are part of intricate epigenetic and neuroendocrine networks [3, 4]. MKRN3, a maternally imprinted gene located in the Prader-Willi syndrome region, acts as a pubertal inhibitor. Its loss-of-function mutations are now recognized as the most common genetic cause of familial CPP [5, 6]. DLK1, another imprinted gene, also contributes to CPP through its regulatory impact on neuroendocrine signalling and hypothalamic plasticity [3].

Equally important is the role of neuropeptides—particularly kisspeptin, neurokinin B, and dynorphin, which orchestrate the reactivation of GnRH neurons. Kisspeptin, encoded by the KISS1 gene, is the most potent known stimulator of GnRH secretion, and its activity is modulated by interactions with neurokinin B and dynorphin in KNDy neurons located in the arcuate nucleus [2, 4]. These neuropeptides not only regulate pubertal initiation but also serve as potential biomarkers for the diagnosis and treatment monitoring of CPP. For instance, recent clinical data have shown that serum kisspeptin and DLK1 levels decrease and increase, respectively, during effective GnRH analogue therapy, suggesting their utility in treatment monitoring rather than diagnosis [7].

Given the complexity of CPP's pathophysiology, a multidimensional approach that integrates genetic testing and neuropeptide profiling is becoming increasingly relevant. Traditional diagnostic methods such as GnRH stimulation tests and imaging are essential, yet they often fall short in distinguishing borderline cases or predicting treatment response. Genetic screening for MKRN3 or DLK1 mutations and neuropeptide measurements may offer earlier detection, greater diagnostic accuracy, and personalized therapeutic strategies.

This review aims to synthesize the latest findings on the genetic and neuropeptidergic mechanisms underlying CPP in girls. By exploring their roles in diagnosis and treatment, this paper will highlight current gaps, propose future

directions, and evaluate the potential of emerging biomarkers and molecular therapies. Understanding these molecular underpinnings is crucial for the evolution of precision medicine in paediatric endocrinology.

1. Genetic Basis of Precocious Puberty

1.1. General Genetic Overview

Pubertal timing is a complex trait influenced by genetic, environmental, and nutritional factors. Twin and familial studies have shown that genetics accounts for 50–80% of the variability in pubertal onset [3, 8]. CPP results from premature activation of the hypothalamic-pituitary-gonadal (HPG) axis. While most cases of CPP in girls are idiopathic, monogenic causes have increasingly been identified, particularly involving imprinted genes and key regulatory pathways of GnRH secretion [4].

1.1.i. MKRN3 Details (Mechanism, Prevalence)

Makorin Ring Finger Protein 3 (MKRN3) has emerged as the most common monogenic cause of familial CPP. *MKRN3* is a maternally imprinted, paternally expressed gene located in the Prader-Willi syndrome critical region on chromosome 15q11-q13. Loss-of-function mutations in MKRN3 lead to early reactivation of the GnRH pulse generator [9]. MKRN3 encodes a zinc finger protein with E3 ubiquitin ligase activity, thought to inhibit pubertal onset by repressing the transcription of GnRH and other pubertal activators [10, 11].

In clinical studies, MKRN3 mutations account for 33–46% of familial CPP cases and around 3.9–9% of sporadic cases [8, 11]. Girls with MKRN3 mutations present with earlier breast development, advanced bone age, and higher basal FSH levels compared to those without mutations. Notably, mutations are paternally inherited due to genomic imprinting, highlighting the importance of detailed family history in clinical assessments.

1.1.ii.DLK1 and Other Imprinted Genes

Delta-Like 1 Homolog (*DLK1*), another maternally imprinted, paternally expressed gene located on chromosome 14q32, has been implicated in both syndromic and non-syndromic CPP [12, 13]. *DLK1* encodes a transmembrane protein involved in Notch signalling inhibition, with roles in adipogenesis, neurogenesis, and hypothalamic development. Loss-of-function mutations in *DLK1* disrupt hypothalamic regulation of GnRH secretion.

Patients with *DLK1* mutations often exhibit CPP alongside metabolic derangements, including obesity and insulin resistance, due to DLK1's regulatory role in adipocyte differentiation [11]. Studies indicate that DLK1 mutations are rare but clinically significant, with a strong paternal inheritance pattern.

1.1.iii.Rare Mutations (KISS1, KISS1R, etc.)

Activating mutations in the KISS1 gene, encoding kisspeptin, and its receptor KISS1R (GPR54) are rare causes of CPP. These mutations enhance kisspeptin signalling, leading to premature GnRH secretion [8, 14]. Only a handful of cases have been described worldwide, reflecting the rarity of these mutations in comparison to MKRN3 and DLK1-related CPP. Furthermore, polymorphisms in PROKR2 and LIN28B, though less frequently, have also been associated with pubertal timing disorders, suggesting a broader genetic landscape.

1.2.Epigenetics in Pubertal Timing

Epigenetic mechanisms, including DNA methylation, histone modifications, and non-coding RNAs, play crucial roles in regulating the onset of puberty. During childhood, the KISS1 and GNRH1 genes are silenced through methylation and Polycomb repressive complexes. Puberty initiation

involves a shift towards active chromatin states, with loss of repressive marks and gain of activating histone modifications [4, 15].

Emerging evidence also links imprinted genes and epigenetic dysregulation with CPP. For instance, hypomethylation of DLK1 regulatory regions has been identified in patients with Temple syndrome, further supporting an epigenetic contribution to pubertal timing [16].

1.3. Genetic Testing and Clinical Relevance

Genetic testing is increasingly integrated into the diagnostic workup for CPP, particularly in familial cases or when associated with syndromic features. Targeted sequencing of MKRN3, DLK1, and KISS1/KISS1R genes can elucidate the aetiology in up to 30–40% of familial CPP cases[17]. Chromosomal microarrays and whole-exome sequencing are useful in complex cases, revealing both sequence variants and copy number changes.

Clinically, identifying a genetic reason aid in prognostication, informs family counselling, and can direct therapeutic choices. For example, MKRN3-mutated individuals typically respond well to GnRH analogue therapy, whereas DLK1 mutation carriers require monitoring for metabolic complications [15-17].

Ethical considerations in paediatric genetic testing, including consent and psychosocial impacts, necessitate comprehensive genetic counselling pre- and post-testing.

2. Role of Neuropeptides

2.1. Hypothalamic-Pituitary-Gonadal (HPG) Axis: Normal Regulation and Timing of Puberty

The initiation of puberty involves the complex activation of the hypothalamic-pituitary-gonadal (HPG) axis. In early life, GnRH neurons are

active but subsequently become quiescent during childhood. Pubertal reactivation of GnRH pulsatility is critical for initiating the cascade of endocrine events leading to sexual maturation [18].

The key to pubertal onset is the increased pulsatile release of GnRH, which stimulates the pituitary to release luteinizing hormone (LH) and follicle-stimulating hormone (FSH). These hormones act on the gonads to produce sex steroids—testosterone in males and oestradiol in females—thus promoting the development of secondary sexual characteristics [18,19].

The central players that govern this reactivation are kisspeptin and neurokinin B, acting upstream of GnRH neurons and forming a critical regulatory network.

2.2. Kisspeptin, Neurokinin B, and GnRH: Molecular Drivers of Puberty

Kisspeptin (encoded by KISS1) and its receptor GPR54 (KISS1R) are pivotal in the control of GnRH secretion. Experimental knockout models in mice have demonstrated that the absence of kisspeptin or its receptor leads tohypogonadotropic hypogonadism, highlighting their indispensable role [19, 20].

In humans, kisspeptin levels increase significantly during puberty, particularly in girls with central precocious puberty (CPP)[21]. Kisspeptin directly stimulates GnRH neuron firing, thereby promoting gonadotropin release. This stimulation is finely tuned by neurokinin B and its receptor NK3R, which act as upstream modulators within the hypothalamic arcuate nucleus [19].

Recent discoveries from experimental models suggest a cooperative role of kisspeptin, neurokinin B, and dynorphin (collectively known as KNDyneurons) in regulating the pulsatile secretion of GnRH. Disruption in any of these neuropeptides' signalling pathways results in impaired reproductive function, as shown in both animal studies and rare human mutations [19; 20].

In addition to genetic studies, experimental models using kisspeptin analogues have provided further insights. Administration of kisspeptin induces LH secretion in children with suspected CPP, making it a potential diagnostic tool [21].

2.3. Clinical and Therapeutic Relevance

The measurement of circulating kisspeptin levels is an emerging biomarker for the activation of the HPG axis. In girls with CPP, serum kisspeptin levels are significantly higher compared to age-matched prepubertal controls [21]. However, challenges remain due to the peptide's pulsatile secretion and rapid degradation, which complicate its routine clinical measurement [18].

Some studies have also investigated neurokinin B concentrations, but their clinical utility is less established compared to kisspeptin [21].

The therapeutic potential of neuropeptide modulation is under active investigation. Kisspeptin antagonists are being developed as potential therapies for conditions characterized by premature activation of the HPG axis, such as CPP. Conversely, kisspeptin agonists might be beneficial in cases of delayed puberty or hypogonadotropic hypogonadism[20].

Neurokinin B antagonists, such as Fezolinetant, have been studied mainly for menopausal hot flashes but are also being explored for their role in modulating GnRH pulsatility in puberty and reproductive disorders [18].

3. Diagnosis and Management of Precocious Puberty in Girls

The diagnosis of central precocious puberty (CPP) begins with a detailed history and physical examination. Key features include the early appearance of secondary sexual characteristics—such as breast development before 8 years of age in girls—and accelerated linear growth velocity [22, 23].

Anthropometric measurements, including growth velocity and pubertal staging based on Tanner criteria, are essential. Signs like breast development (thelarche) and pubic hair (pubarche) are assessed, alongside bone age determination using left-hand radiographs. An advanced bone age greater than chronological age suggests premature activation of the hypothalamic-pituitary-gonadal (HPG) axis [21-23].

Initial biochemical evaluation includes basal luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels using ultrasensitive assays. A basal LH >0.3 IU/L suggests HPG axis activation [23]. If basal levels are inconclusive, a GnRH stimulation test is performed; a stimulated LH peak >5 IU/L confirms CPP [24].

Serum estradiol levels, although variable, can support the diagnosis. However, hormonal assays alone may be insufficient, particularly in early pubertal stages.

Pelvic ultrasound (PU) serves as a valuable, non-invasive diagnostic tool, with key parameters including uterine volume >2.0 mL, uterine length >34 mm, ovarian volume >2.0 mL, the presence of multiple ovarian follicles (>4 mm diameter), and endometrial thickness >2 mm as an indicator of oestrogen exposure[24].Girls with CPP demonstrate significantly larger uterine and ovarian volumes compared to prepubertal peers. A uterine volume >2.0 mL and an ovarian volume >2.0 mL is associated with good sensitivity (88.8%) and specificity (89.4%) for CPP [23, 24].If pelvic ultrasound findings are suggestive of CPP but confirmation is needed, brain MRI should be performed—especially in girls under 6 years or in cases with neurological signs—to exclude CNS abnormalities [23].Genetic testing is recommended for familial cases of CPP, particularly when paternal inheritance is evident, to identify mutations in MKRN3 or DLK1 [22].

3.2. Management Strategies

The primary treatment for CPP is long-acting gonadotropin-releasing hormone analogs (GnRHa), which desensitize GnRH receptors and suppress the HPG axis [24]. Therapy aims to halt progression of puberty, optimize final adult height, and address psychosocial concerns [22, 23].Available formulations include monthly, three-month, and six-month depot injections (e.g., leuprolide acetate), as well as histrelin subcutaneous implants with a duration of 12–24 months [25].Indications for therapy include girls diagnosed under 6 years of age, rapid progression in those aged 6–8 years, significant psychosocial distress, and compromised predicted adult height[23-25].Initiating therapy before 6 years of age predicts the greatest gain in final adult height, while benefits in older girls (8–9 years) are less certain and require individualized decisions; monitoring includes growth velocity assessment every 3–6 months, annual bone age evaluation, and periodic hormonal assays to confirm suppression.Pelvic ultrasound is useful for monitoring regression of uterine and ovarian size during therapy. A decrease in uterine and ovarian volumes and endometrial thickness reflects effective suppression [24].GnRHa therapy is typically discontinued when the child reaches an appropriate bone age (~12 years) to allow normal pubertal progression [25].Despite significant advancements in understanding the pathophysiology and management of central precocious puberty (CPP), several challenges remain.

4.1. Diagnostic Challenges

The clinical presentation of CPP overlaps with benign variants such as premature thelarche and premature adrenarche, complicating early diagnosis. Although ultrasensitive LH assays and GnRH stimulation tests have improved diagnostic accuracy, variability in assay sensitivity and the pulsatile nature of hormone secretion limit reliability. Moreover, pelvic ultrasound measurements,

while helpful, have overlapping parameters between early CPP and non-progressive conditions, particularly at early pubertal stages [24].

Genetic testing has illuminated the role of imprinted genes such as MKRN3 and DLK1, but these mutations explain only a subset of familial CPP cases. The discovery of additional genetic and epigenetic regulators is necessary to fully elucidate the aetiology of CPP, especially in sporadic cases [4].

Furthermore, brain MRI screening practices remain debated in girls aged 6–8 years with isolated early breast development and no neurological signs, due to the low yield of pathological findings and concerns over cost-effectiveness and sedation risks [23].

4.2. Treatment Challenges

While GnRH analogues (GnRHa) effectively halt pubertal progression and improve predicted adult height in young children, the benefit is less certain in girls diagnosed after age 8. Studies show that older girls derive only modest height gains, raising questions about the cost-benefit ratio in these cases [26].

Another concern is the impact of GnRHa therapy on body mass index (BMI) and long-term metabolic health. Although short-term studies indicate no significant increase in BMI, long-term data are limited, and potential risks of obesity, insulin resistance, and cardiovascular disease remain a focus for future research [23].

Additionally, the psychosocial impact of CPP, including increased rates of depression, low self-esteem, and social withdrawal, is well-documented. However, evidence supporting the psychosocial benefits of GnRHa therapy is inconclusive. Well-designed longitudinal studies are needed to evaluate whether treatment improves mental health outcomes and quality of life.

5.3. Future Perspectives

Future Directions

Advances in genomic technologies, such as whole-exome and whole-genome sequencing, promise to uncover novel genes and pathways implicated in pubertal timing. Integration of epigenetic profiling may reveal how environmental exposures influence pubertal onset, offering new targets for intervention [4].

While promising, the application of neuropeptide measurements and therapies in clinical practice requires further validation. Large-scale longitudinal studies are needed to establish normative ranges and predictive values of kisspeptin and neurokinin B for pubertal disorders.

In therapeutics, there is growing interest in kisspeptin antagonists and neurokinin B modulators as potential alternatives to GnRHa, aiming to provide more physiological regulation of the HPG axis. Clinical trials exploring these agents could offer future options for selective, reversible suppression of puberty with fewer side effects [19].

From a public health perspective, early-life interventions to address childhood obesity and environmental exposures may help mitigate the secular trend of earlier pubertal onset observed globally.

Finally, development of personalized medicine approaches—considering genetic, hormonal, and psychosocial profiles—could enable individualized diagnosis and treatment plans, optimizing outcomes for girls with CPP.

6. Conclusion

CPP arises from a multifactorial interaction of genetic, epigenetic, and neuroendocrine factors, with key roles identified for MKRN3, DLK1, and kisspeptin signaling pathways. Advances in diagnostics—including hormonal

assays, pelvic ultrasound, and genetic testing—have improved accuracy in differentiating CPP from benign variants. Timely initiation of GnRH analogue therapy remains the gold standard, significantly enhancing final adult height, especially when started before 6 years of age. Ongoing challenges include optimizing treatment thresholds and addressing the psychosocial burden of early puberty.

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