

Central Precocious Puberty: From Genetics to Treatment

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Abstract: Central precocious puberty (CPP) results from early activation of the hypothalamic - pituitary -gonadal (HPG) axis and follows the same sequence as normal puberty. While many factors involved in pubertal initiation remain poorly understood, the kisspeptin system is known to play a key role. Currently, mutations in the kisspeptin system, *MKRN3*, and *DLK1* have been identified in sporadic and familial cases of CPP. The diagnosis is based on physical exam findings indicating advancing puberty and on laboratory tests confirming central HPG axis activation. GnRH analogs are the mainstay of treatment and are used with the goal of height preservation. Newer extended release formulations continue to be developed. Currently there is no evidence of long-term complications associated with treatment. However, many areas remain to be explored such as targeted therapies and aspects of clinical management. Further investigation into psychological effects and additional data regarding long-term outcomes, particularly in males, is needed.

Key words: Central precocious puberty, etiology, genetics, treatment, outcome

Precocious puberty is defined as “the development of puberty younger than that which is expected for ethnicity and race” [1]. Two to 2.5 standard deviations younger than the mean is typically the accepted threshold for making the diagnosis [2]. Thus, puberty is considered early if it commences prior to age 8 in Caucasian and 7 ½ in Hispanic and African American girls, and earlier than age 9 in boys. A Danish study estimated precocious puberty—which included common variants as well as bonafide central precocious puberty (CPP)—at a prevalence of 0.2% of girls and less than 0.05% of boys [3]. Another study, which was limited to those with CPP and those who had presented to a tertiary care center, estimated the incidence at 1.1 per 100,000 girls [4]. Here, we will discuss the etiology and diagnosis of CPP including new information regarding the genetic mutations that have been implicated in sporadic and familial cases. Current treatment options along with their indications, considerations, side effects and outcomes will be reviewed. Finally, we will consider potential areas of future research.

I. Normal Puberty: Molecular Mechanisms and Physiology. The exact signal and cause of pubertal initiation remains a mystery. However, it is known that genetics plays a primary role with contributions from the environment, nutrition and sex. Pubertal onset is also closely coupled to skeletal maturation, although exactly how bone age and HPG axis activation are linked is enigmatic and poorly understood [5]. However, conditions in which advanced skeletal maturation occurs are associated with earlier onset of central puberty, such as in poorly controlled congenital adrenal hyperplasia

Several key players in the initiation of puberty have been identified. One of these is kisspeptin, a peptide hormone expressed in the hypothalamus, adrenal glands and pancreas [6]. In the hypothalamus, it serves as a ligand for the kisspeptin receptor, KISS1R, which is a G- protein

coupled receptor present on GnRH secreting neurons [7]. As kisspeptin levels increase, the amplitude and frequency of GnRH pulsatility is augmented [7]. For each Tanner stage, girls tend to have higher kisspeptin levels than boys, which may explain the earlier pubertal timing seen in females. As discussed in the genetics section, both elevated kisspeptin levels and mutations associated with increased kisspeptin signaling are associated with CPP [7]. Upstream of kisspeptin signaling is another neuropeptide, neurokinin B, which acts through its receptor NK3R. Neurokinin B is thought to act in concert with the kisspeptin system as an essential gatekeeper of puberty [8]. In addition to these hypothalamic molecules, peripherally produced hormones such as leptin and insulin are also thought to be important modulators of the timing of pubertal onset.

II. Central Precocious Puberty: Etiology and Diagnosis

A. Etiology. Approximately 90% of girls and 25%-60% of boys with CPP have an idiopathic cause [9, 10]. The pathologic etiologies are similar for boys and girls [1]. Several known potential causes and conditions associated with an increased risk of CPP are listed in Table 1 [1, 11]. In one cohort study of 176 children with hypothalamic-pituitary lesions, endocrine disorders were diagnosed prior to any neurological symptoms in 2/3rds of affected individuals, of whom 20% presented with CPP [12]. International adoption is well established as a risk factor for CPP, although the exact reason is unclear. It is thought that transitioning from a nutrition-poor environment to one of nutritional excess can trigger puberty in some children [1]. A family history of CPP is another risk factor and is discussed in more detail below.

The identification of monogenic causes of CPP is one of the most exciting areas within pediatric endocrinology. Thus far, mutations in four distinct genes have been identified in patients and families with a history of CPP. Naturally, this number is expected to increase as further

sequencing and genetic studies are undertaken in affected individuals, thereby resulting in a declining number of “idiopathic” cases. Gain-of-function mutations have been described in both kisspeptin and its receptor, *KISS1R* [13, 14]. In described cases, the patients were heterozygous, which corresponds with the autosomal dominant pattern seen in familial CPP [15]. However, kisspeptin and *KISS1R* mutations appear to account for very few cases as large-scale studies in children with CPP have failed to identify additional individuals harboring abnormalities in these genes [15].

Another genetic abnormality linked to CPP involves the Makorin RING-finger protein 3 (*MKRN3*) gene. In the native state, *MKRN3* appears to act as an inhibitor of puberty. Expression is high in the hypothalamic arcuate nucleus in prepubertal mice, decreases prior to puberty, and is low after puberty [16]. Thus, in contrast to the gain-of-function mutations associated with kisspeptin and *KISS1R* genes, it is loss-of-function mutations in *MKRN3* that are associated with CPP. While the exact function of *MKRN3* is not yet fully understood, one group demonstrated that it polyubiquitylates *Nptx1*, another protein of undetermined function that is highly expressed during puberty [17]. Since polyubiquitinylation typically leads to protein degradation, *Nptx1* levels are normally kept low pre-pubertally, but then rise once *MKRN3* levels decrease as puberty commences. One group [16] studied 15 families with a history of CPP and found mutations in *MKRN3* in one-third of them leading to truncated proteins or to missense mutations predicted to disrupt protein function. Since then, at least 10 different genetic defects have been described, all of which are loss-of-function mutations resulting from frameshift, missense or nonsense mutations [18]. *MKRN3* is maternally methylated, and thus only the paternal gene copy is expressed [18]. This explains the observed paternal inheritance that is transmitted in an autosomal dominant pattern. In one study of 20 boys with idiopathic CPP who underwent genetic analysis, 8 of them had *MKRN3* mutations and 1

had a KISS1-activating mutation [19], indicating that MKRN3 mutations are likely involved in a relatively large percentage of “idiopathic” cases.

Delta-like homolog 1 (DLK1), another paternally expressed imprinted gene, is the fourth and final gene discovered thus far to be implicated in the pathogenesis of CPP. This gene encodes a protein expressed in the hypothalamus and kisspeptin-expressing neurons [20]. DLK1 is a part of the delta-notch pathway, which is an evolutionarily conserved signaling pathway with roles in proliferation and differentiation during development [21]. Notch ligands bind to the notch receptors, which causes a cascade leading to transcription of target genes [21]. There are 5 activating canonical ligands as well as noncanonical ligands of which DLK1 is one [22]. Loss-of-function mutations in this pathway are often embryonically lethal [22]. In the pituitary, DLK1 and notch signaling appears to play a role in pituitary cell type differentiation [21]. DLK1 was implicated in the genesis of CPP when a family with 5 affected girls underwent linkage analysis and whole-genome sequencing. A complex mutation was found in which 14kb of DNA were deleted but there was also a 269 bp duplication. No circulating levels of DLK1 were detected in affected individuals [20]. However, when DLK1 gene sequences were examined in 60 girls with idiopathic CPP, none of them had mutations in this gene [23]. Thus, while this study was not adequately powered to definitively state that DLK1 gene mutations as a cause of CPP are rare, it does not appear that they are very common either.

While the absolute number of individuals with CPP found to harbor mutations in the aforementioned genes is small, these discoveries have the potential to yield novel and significant insights into normal reproductive physiology with broader implications in health and disease. Known genetic causes of CPP along with their purported mechanisms of action are delineated in Table 2. Figure 1A illustrates current understanding of the mechanisms involved in pubertal onset and the proteins in which mutations have been implicated as causes of CPP whereas Figure 1B depicts the putative role of MKRN3 in maintaining quiescence of the HPG axis during the prepubertal years.

Practice Points:

- The majority of girls have idiopathic CPP whereas boys are more likely to have a pathological cause
- Identification of monogenic causes of CPP is still in its infancy, but mutations in Kisspeptin, KISS1R, MKRN3 and DLK1 have been reported thus far.

B. Diagnostic Studies and Diagnosis. In addition to a careful history and physical, obtaining a bone age x-ray is often the first step in the evaluation of precocious puberty. If the bone age is more than 2.5 standard deviations advanced, then the child is more likely to have pathologic precocious puberty [24]. However, this is not a fail-proof indicator as children with benign variants can still have significantly advanced bone ages. Regardless of the lack of specificity associated with the bone age, it gives a good indicator of height potential, which may help to guide treatment.

The initial laboratory evaluation includes obtaining serum gonadotropins and sex steroids. However, depending on the assay used and the time of day, random values may not be informative and care must be taken in interpretation of results. Serum LH levels are ideally obtained in the morning and measured using an ultrasensitive methodology, such as immunochemiluminescence, that has a lower limit of detection of 0.1mIU/L [9, 25]. LH concentrations <0.3 mIU/L are in the prepubertal range whereas levels >0.3 mIU/L are usually indicative of puberty [10]. However, these levels need to be taken in context as children with slowly or intermittently progressive CPP can have levels in the pubertal range as can young girls under the age of 2 years who are in the mini-puberty of infancy [26]. Likewise, ultrasensitive LH levels may be prepubertal in children with unequivocal but early CPP [9].

FSH levels are typically of limited diagnostic usefulness [9]. Even using sensitive assays such as tandem mass spectrometry, definitive threshold concentrations for prepubertal vs. pubertal levels

have not yet been determined for many hormones [25, 27]. Regardless, suppressed gonadotropins and elevated sex steroids would indicate that a form of peripheral, rather than CPP is present [25].

When CPP is suspected but the LH concentration is equivocal, a GnRH stimulation test should be performed [10]. Historically, this was accomplished by giving synthetic GnRH, which is no longer available in the United States. GnRH analogs (GnRHAs) such as leuprolide acetate are an acceptable and established substitute. Different protocols exist regarding the timing and number of LH and FSH measurements [28, 29]. Regardless of the protocol used, pubertal individuals have a stimulated peak LH of at least ~4-6 mIU/L whereas prepubertal children will have a minimal increase from baseline [25]. The stimulated LH/FSH ratio can help to distinguish between progressive puberty versus nonprogressive variants, with a ratio greater than 0.66 indicating puberty in girls [30, 31]. If there is an equivocal result, the child should be monitored for another three to six months and re-assessed for pubertal progression [24]. While generally not used in the clinical setting, LH levels in a first morning void have been shown to correlate with pubertal status and can therefore be useful as adjunctive information.

Whether to obtain an MRI in all girls diagnosed with CPP has long been an area of controversy. Ng and colleagues [32] performed a retrospective study of 67 females who presented with CPP and found that 15% had intracranial abnormalities. Another study including 229 girls with CPP revealed that 6.3% had an unsuspected pathological finding and that all were older than 6 years. They concluded that all girls younger than age 8 and presenting with CPP should have a brain MRI [33]. In 2009, 30 international experts convened to address topics surrounding CPP, with brain imaging as one such area. They determined that without clinical neurological findings or rapid pubertal progression, the incidence of pathological brain findings in girls decreases with age [9]. A review of the major papers on CPP found that while CNS abnormalities are noted in 8-15%, new findings requiring intervention in females aged 6-8 only occurred in 0-2% [34]. Thus, it has been

suggested that in otherwise asymptomatic girls with CPP, a discussion occur with the parents regarding the pros and cons of imaging. Brain MRIs are recommended for all boys presenting with CPP [9].

An additional option for imaging in girls is pelvic ultrasound which can provide useful information if clinical and biochemical features are equivocal [27].

The role of genetic testing in CPP is an evolving area. However, as commercial test availability for mutations in genes implicated in CPP increases, the cost of such investigation will need to be balanced with the benefit of the information gleaned. Notable, a recommendation to undertake genetic testing has already made its way into some diagnostic algorithms intended to be used in the clinical setting [35].

Practice Points:

- Ultrasensitive LH is more clinically useful than FSH to diagnose precocious puberty. Gonadotropins and sex hormones can help to distinguish central from peripheral precocious puberty.
- GnRH stimulation test should be used in diagnostically equivocal cases.
- Brain MRI should be obtained in all boys with CPP
- MRI in girls is more controversial, with earlier age more clearly necessitating brain MRI.

III. Treatment

A. Goals of treatment. The main goal of treatment in children with CPP is to preserve adult height [9]. However, several cautions are worth noting. One is that the amount of height gained is highly variable and closely related to the age at which treatment is started, especially in girls [24]. An additional caveat is that height outcomes are usually based on the difference between predicted

adult height at baseline and treatment end [24]. This is intrinsically flawed as many studies have demonstrated that height predictions routinely over predict actual adult heights in children with CPP [24]. Therefore, providers have limited ability to accurately estimate the height outcome for any individual patient with CPP.

Understandably, many parents are dismayed and fearful when they see signs of early puberty in their children. One article recounts a parent's perspective and notes that their daughter "suffers" from precocious puberty "despite puberty being a normal process" [36]. This, coupled with reports demonstrating poorer psychological outcomes amongst those with either precocious puberty or earlier menarche, has prompted some to consider psychological distress as one reason to halt puberty in children with CPP [9, 10, 37]. However, other studies have failed to find any differences in psychological functioning in girls with CPP compared with controls [38, 39]. The literature on this topic is conflicting and rife with methodological problems. Thus, evidence regarding psychological benefit from treatment was deemed inconclusive by the GnRHa Consensus Conference, and more research in this area has been recommended [9].

B. Treatment options. Girls with CPP who are treated prior to age 6 have the greatest gains in adult height whereas those treated between ages 6 and 8 years have a variable and moderate response [1, 40-43]. There is no benefit from treatment in terms of height in girls who are \geq age 8 [1, 43]. Notably, there are insufficient data to establish analogous age guidelines regarding treatment in boys. The GnRHa Consensus Group recommended that treatment decisions in girls with pubertal onset after age 6 be individualized but that therapy should be considered in all boys prior to age 9 with evidence of compromised height [9].

The standard of care for the treatment of CPP is a GnRHa. Many different preparations of GnRHAs exist, with different routes of administration and durations of effect [9]. A long-acting

GnRHa in the form of monthly intramuscular leuprolide acetate was prescribed almost exclusively for the treatment of CPP in the U.S. for many years [9]. However, the development of even more potent extended-release forms of GnRHAs has been a burgeoning area of investigation, and several additional therapeutic options are now available. Three-monthly depot preparations, also administered via intramuscular injection, have also been used to treat CPP [44]. Several studies have suggested that the degree of biochemical suppression achieved with 3-monthly dosing is consistently less than that seen with monthly GnRHa administration [1, 42, 44-47]. Nonetheless, the clinical response to treatment appears to be equivalent although minimal comparative information is available. The most recent arrival on the scene of extended-release injectable GnRHAs is a 6-monthly preparation which has been touted as effective and safe in children with CPP [48]. Additional 6-monthly forms of GnRHa are being explored and initial results appear promising. A final member of the therapeutic armamentarium is the histrelin subcutaneous implant. The implant allows for sustained release of the potent GnRHa histrelin, and requires a minor outpatient surgical procedure for implantation and removal, usually performed under local anesthesia [49]. A rapid and profound suppression of the HPG axis occurs by one month following placement [50]. Although marketed to be replaced annually, the device contains ample medication to suppress puberty for at least 2 years [51]. Despite these innovations, GnRHAs remain prohibitively expensive which represents a significant barrier to care for some families.

Treatment is considered successful if pubertal progression is halted and if growth velocity and the rate of skeletal maturation are slowed. Due to an initial flare in HPG axis activation when treatment with a GnRHa is initiated, vaginal bleeding sometimes occurs in the setting of significantly advanced pubertal development at baseline [9]. However, this is typically limited to 1 or 2 episodes at the most. At present, no uniform consensus exists as to the optimal strategy for monitoring treatment in CPP beyond auxological parameters and periodic bone age x-rays. Importantly,

ultrasensitive LH levels often fail to revert to prepubertal values in children who are fully suppressed on GnRHa therapy. Thus, the finding of a random pubertal ultrasensitive LH is not necessarily indicative of lack of treatment efficacy, and a GnRHa stimulation test should be performed for definitive information if clinical criteria are concerning [52].

Practice Points:

- Girls <6 years old benefit most from treatment. Less data exists for boys but treatment should be considered <9 years old.
- GnRHAs are the standard treatment, with different formulations available.

C. Safety and adverse effects. Overall GnRHAs have a remarkable track record of safety and efficacy. The most commonly reported side effects are minor and nonspecific such as headaches or hot flashes. Approximately 10-15% of treated individuals are affected by local skin reactions at the site of depot injections. Rarely, sterile abscesses have been reported and mandate a change in treatment modality. The histrelin implant has a propensity to become brittle and break upon removal, sometimes necessitating ultrasound guided extraction of the fragments [49].

D. Outcomes. The main targeted outcome of treatment is the preservation of height potential. However, reproductive, metabolic and bone mineral density are also outcomes of interest. One study noted a 14.1 cm difference in height between treated and untreated girls who presented prior to age 5 compared with a 4.2 cm difference in those older than 5 years [53]. In another study, there was a 2.7 cm net gain in height when girls were treated prior to age 6 and a 1.9 cm net gain in height when they were treated after age 6 [24]. Stopping GnRHa treatment at age 11 and a bone age of 12 has been associated with the greatest adult height [42]. However, given that a bone age of 12 could be associated with a wide range of chronological ages, the bone age has to be taken in context within

the whole clinical situation. Furthermore, bone age does not necessarily predict the gain in height after cessation of treatment [9].

Regarding reproductive function, menses in girls begins 2 to 61 months (mean of 16 months) after stopping treatment [9]. The interval of time from cessation of treatment to menarche appears to be inversely proportion to the age at which therapy is stopped [54, 55]. Thus far the incidence of regular cycles and pregnancy attainment in women with a history of CPP are commensurate with the general population [9]. While some investigators have found no differences between treated and untreated women with regard to indices of fertility, others have noted lower spontaneous pregnancy rates in untreated women, suggesting that GnRHAs may actually exert a protective effect in this regard [56]. There is currently no information on ovarian reserve and age of menopause in either treated or untreated women with a history of CPP. Data on outcomes in boys is sparse but thus far there appears to be no difference in sperm counts and gonadal function in young adult men who had CPP compared with the general population [57, 58].

It has been suggested that women with a history of CPP are at increased risk for polycystic ovarian syndrome (PCOS). One study found clinical evidence of PCOS in 41% of girls with CPP within 4 years after menarche [59]. A further investigation of 46 women with a history of treated CPP demonstrated a 32% prevalence of PCOS at a mean age of 18.1. However, other studies have failed to find evidence of an increased risk of PCOS in women with a history of CPP [9]. On average, girls with CPP have higher BMIs than their non-affected counterparts and in some studies, also have markers of insulin resistance. In contrast, BMIs remain stable during GnRH α treatment and some studies have found equivalent measures of body composition in women with or without a history of CPP [9]. Taken together, there is some evidence of an increased risk of PCOS in girls with a history of CPP, but further studies are needed to establish a definitive association.

Bone mineral density is another area of interest when contemplating the long-term follow-up of GnRHa treatment. In adults, GnRHAs cause a hypogonadal state, which in turn leads to decreased bone mineral density and increased fracture risk [60]. As one might expect, bone mineral density is increased at baseline in girls with CPP as compared with controls [61]. During GnRHa treatment, bone mineral density declines but recovers to that of age-matched controls within a few years post-treatment [41, 62, 63]. On balance, information pertaining to outcomes of GnRHa therapy when used for CPP are highly reassuring. Whether the disparate GnRHa formulations being used today will result in differential outcomes remains to be seen.

Practice Points:

- Height potential varies widely based upon age of presentation and treatment, bone age and age of stopping treatment.
- There does not appear to be any long-term adverse reproductive effect of treatment and some evidence indicates it could be beneficial.
- Some evidence of increased PCOS, but this is still preliminary and not definitive.
- No definitive evidence of long-term bone mineral density differences in treated children.

IV. Future Directions

A. Alternative therapeutic approaches. Currently the only option for the treatment of CPP is a GnRHa. It has long been recognized however that these agents result in an initial flare in activation of the HPG axis which is considered a downside to their use [9]. Although a pure GnRH antagonist would avoid this issue, none have been found to be safe and effective in the setting of CPP. Another therapeutic strategy might be to target the kisspeptin system using either an agonist or antagonist. Based on animal studies, such an approach would render LH concentrations within a physiologic

rather than a sub-physiologic range which might have advantages in terms of linear growth [64]. To date, no medication that targets the kisspeptin system has been developed that is ready for prime time in the clinical arena. .

Given the more recent revelations of specific genetic etiologies of CPP, it is tempting to speculate in what way these discoveries could be exploited for the development of more precise targeted therapies. Given the role of wild-type Mkrn3 in polyubiquitinylation of Nptx1, targeting the ubiquitin pathway could conceivably be a treatment for Mkrn3-related cases of CPP. Proteasome inhibitors can inhibit this pathway. Bortezomib and Carfilzomib are two FDA-approved proteasome inhibitors that are used to treat multiple myeloma, demonstrating that the ubiquitin pathway can successfully be used as a disease target [65]. In the case of Mkrn3 mutations associated with CPP, though, deubiquitinases would need to be targeted, which would result in an increased lifespan of ubiquitin-Nptx1 proteins. Currently there are deubiquitinase inhibitors being used in research but none have yet been tested in clinical trials [65].

Targeting the Notch pathway in the context of DLK1 could conceivably be another target. In fact, using Notch inhibitors is an area of active research in cancer pharmacogenetics [22]. However, whereas the Notch pathways are blocked in cancer treatment, the defect in CPP appears to be a lack (i.e. underactivity) of the noncanonical Notch ligand, DLK1. Thus, while it remains a potential therapeutic option, care would have to be taken that stimulating the Notch pathway does not have an unintended increased risk of malignancy. Additionally, it does not appear that DLK1 mutations underlie a large number of CPP cases, make this a less attractive option.

B. Future Research. In addition to exploring alternative treatments, multiple other areas within the field of CPP merit further study. The psychological correlates of either treated or untreated CPP are poorly understood and badly in need of additional investigation. Many of the studies regarding

effects of early puberty are gleaned from girls experiencing puberty within the normal age range, but earlier than average. Whether and in what way those results can be extrapolated to girls with CPP is unknown.

Additional long-term follow up is needed to expand current knowledge of reproductive function and risk of PCOS in women. Likewise, additional follow up data in boys are essential in order to advance our limited understanding of the implication of CPP in males and to assist with making treatment decisions in idiopathic cases.

Research Agenda:

- Mechanistically targeted therapies should be pursued, especially with respect to the kisspeptin system and to ubiquitinylation system with MKRN3 mutations
- We need better understanding of the psychological effects, if any, of treating or not treating CPP in boys and girls.
- Further evaluation of the long-term consequence of reproductive function and risk of PCOS in women needs to be explored.
- Further studies in boys are needed as there is relatively little information on CPP in boys.

V. Summary. CPP is a condition for which one main treatment modality exists: GnRH agonists. The clinical judgment lies in whether MRI is indicated and in whether to halt puberty or allow its natural progression. While many aspects of CPP are well established, revelatory scientific discoveries continue to be made and many unanswered questions remain, particularly with the genetic underpinnings. Ongoing interrogation of affected individuals and families from the molecular genetic standpoint will enrich our understanding of the pathophysiologic underpinnings of early HPG axis activation and potentially lead to new treatments. Large-scale prospective multicenter studies

employing novel GnRH α formulations will continue to augment our therapeutic armamentarium. Lastly, rigorously conducted large-scale follow-up of both treated and untreated individuals will enhance our ability to provide prognostic information for families and providers.

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Table 1: Causes and Conditions Associated with an increased Risk of Central Precocious Puberty

Idiopathic
Structural or Functional CNS abnormality -arachnoid cyst -hypothalamic hamartoma -hydrocephalus -hypopituitarism
Malignancy -craniopharyngioma -ependymoma -germinoma -low-grade gliomas -astrocytoma -pineal tumor
Paraneoplastic conditions -germ cell tumors (CNS, gonadal, hepatic, mediastinal) -hepatoblastoma
CNS infection and CNS granulomatous disease
Trauma and insults -cerebral palsy -CNS irradiation -intracranial bleeding
Syndromes and Genetic Causes -Neurofibromatosis, type 1 -Tuberous sclerosis -Sturge-Weber syndrome -Gain of function mutations in kisspeptin/kisspeptin receptor -MKRN3 mutations -DLK1 mutations
Environmental -International adoption -withdrawal of chronic sex hormone exposure

Table 2: Known and Potential Genetic Causes of Central Precocious Puberty

Gene	Protein	Function	Reference
Confirmed Causes of Central Precocious Puberty			
KISS1	Kisspeptin	Binds to KISS1 receptor	[14, 66]
KISS1R	KISS1R	G protein-couple receptor, involved in increased GnRH pulsatility	[13, 67]
MKRN3	MKRN3	Ubiquitylation, cell signalling	[16, 17, 68-70]
DLK1	Delta-like homolog 1	Pituitary cell differentiation	[20]
Potential Causes of Central Precocious Puberty that have not yet been validated in humans			
GABRA1	Gamma amino butyric acid A1 receptor α -1 subunit	Puberty acceleration vis kisspeptin	[7]
LIN28B	Lin 28 homolog B	Unknown, homolog of <i>C. elegans</i> protein involved in GnRH secretion	[2, 7, 27]
NPYR	Neuropeptide Y	Antagonizes GABA effects on GnRH neurons	[2, 7, 27]
TAC3 & TACR3	Neurokinin B (NKB) & NKBR	Regulation of GnRH secretion	[7]

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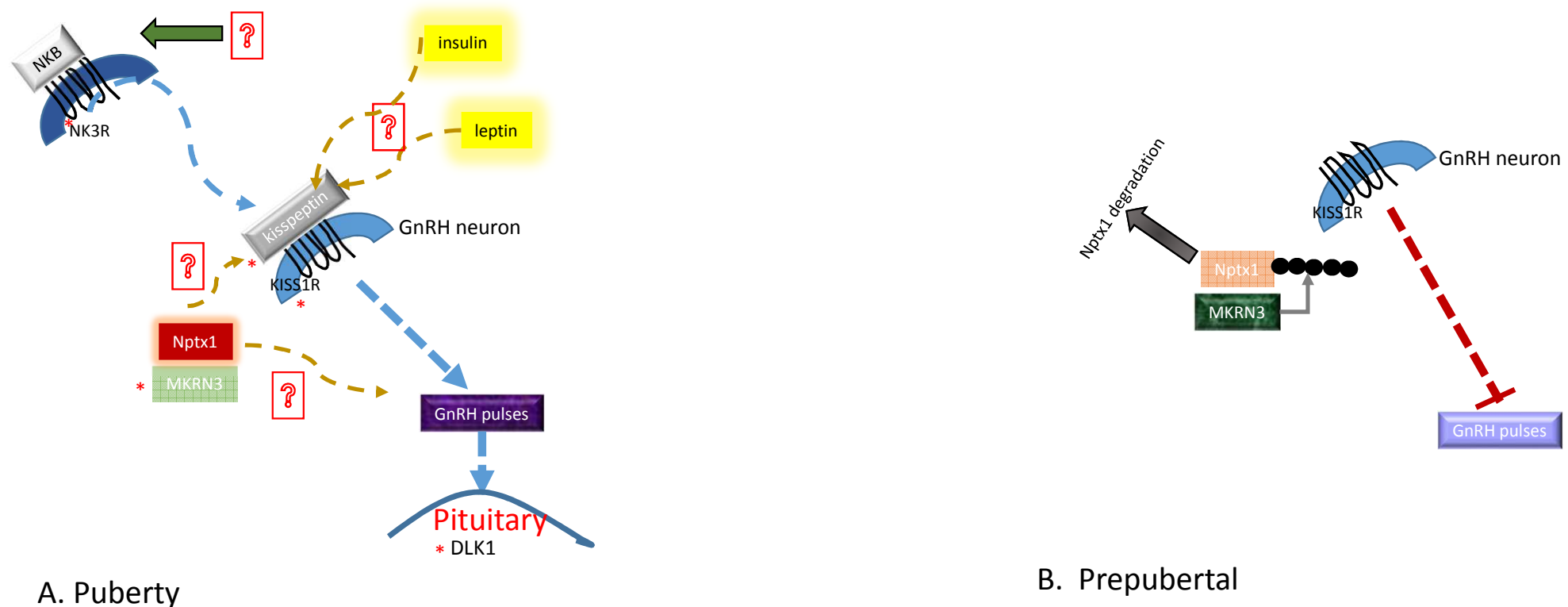


Figure 1. A schematic illustrating some of the key players in puberty initiation. A. Potential roles in puberty initiation. Neurokinin B (NKB) and its receptor NK3R induce GnRH pulses, likely through increased kisspeptin levels. Nptx levels increase during puberty and its levels are inversely associated with MKRN3, although the exact role is still unknown. * Denotes genes in which mutations have been described that have been identified in individuals with CPP. **B. Prepubertal.** The GnRH pulses are largely suppressed. Nptx1 levels are low due to ubiquitinylation by MKRN3, which results in Nptx1 degradation.