

# MAMMALIAN KISSPEPTIN AND PUBERTY: MECHANISM, DETECTION AND RECENT ADVANCEMENTS

## Abstract

This study digs into the complexities of pubertal onset, a critical stage that includes sexual maturation, growth, and the development of secondary sexual features. The highly controlled process involves the Hypothalamic-Pituitary-Gonadal (HPG) axis, which orchestrates pubertal initiation via hormones, neuropeptides, and neurotransmitters such as Kisspeptin. Kisspeptin's involvement in GnRH release and its complex regulation by estrogen, Neuropeptide Y, and miRNAs are investigated. In this intricate network, dysregulation can result in delayed or premature puberty. The work emphasizes the importance of novel detection methods, pointing to early changes in Kisspeptin and GnRH levels, as well as changes in transcriptional component expression patterns, as potential indicators for pubertal start. Because the genetic/familial variables that contribute to pubertal timing are heterogeneous, developing a standard detection method remains difficult, underlining the necessity of multidimensional approaches in understanding and identifying pubertal onset signals.

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Puberty is the phase of attaining sexual maturation, pubertal onset marks the appearance of the first signs of sexual maturation. To have the ability to reproduce one must attain puberty and undergo complete development of sex organs. Most notable changes that occur during the puberty phase are growth in stature and development of secondary sexual characteristics.

The age at which pubertal onset occurs varies across mammalian species and even within the individuals of same species. This difference in onset suggests that it is highly regulated and influenced by multiple factors. By elucidating the multifactorial nature of pubertal initiation, we can get a deeper understanding of reproductive health and potential areas for intervention to better the cause. Pubertal onset is a highly regulated process, getting innervated by hormones, neuropeptides, and neurotransmitters of which some are excitatory or inhibitory (Abreu & Kaiser, 2016). The main regulator of the pubertal onset is the Hypothalamic-Pituitary-Gonadal (HPG) axis (Terasawa & Fernandez, 2001). The HPG axis regulates via release of certain hormones namely Gonadotropin-releasing hormone (GnRH), Luteinizing hormone (LH), Follicular stimulation hormone (FSH) and recently Kisspeptin has also been identified to play a role in regulation of pubertal onset (Uenoyama et al., 2019). Other factors that control pubertal onset include Circadian rhythm, nutritional status, and epigenetic factors. (Tomikawa et al., 2012a) (Lomniczi et al., 2013). Alteration and dysregulation of this factors can lead to either delayed puberty or precocious puberty. GnRH neurons are scattered throughout hypothalamus which gets released in pulsatile manner to activate release of FSH and LH from the pituitary which helps in maturation of sexual organs. Kisspeptin plays a crucial role in release of GnRH from hypothalamus, Kisspeptin is released from the Kisspeptin neurons found within ARC and POA region of the hypothalamus in mammals, ARC Kiss neurons are crucial for activation mechanism of GnRH (Terasawa et al., 2013). Kisspeptin is coded by the gene *KISS1* and its subsequent Kisspeptin 1 receptor is coded by *KISS1R*, a GPR54 receptor. It was firstly reported by (Seminara et al., 2003) and (de Roux et al., 2003) that mutation in the *KISS1R* led to delayed pubertal onset and abnormality in the development.

It was reported that deletion of *Kiss1* or *Kiss1r* gene led to a condition called hypogonadotropic hypogonadism in mice (Lapatto et al., 2007). Kisspeptin is coexpressed with the Neurokinin B and Dynorphin, these neurons are called *KNDy* neurons (Zeydabadi Nejad et al., 2017). Kisspeptin plays major role in estrogen mediated negative and positive feedback of LH release. Poor interaction between kisspeptin and its receptors leads to impaired pubertal onset as suggested in studies. (Skorupskaite et al., 2014). It is reported that Kisspeptin pathway has sexual dimorphism, expression, distribution of fibers and cell bodies vary in male and female (Hrabovszky et al., 2010). Kisspeptin controls various pathways either directly or indirectly, that includes follicular development, oocyte formation, ovulation, embryo implantations and thus acting like one of the major players in pubertal onset. Since Kisspeptin is the major regulator of pubertal onset it is necessary to understand the regulation of Kisspeptin.

## **I. REGULATION OF KISSPEPTIN**

Kisspeptin neurons are scattered around in ARC, AVPV and POA region of the brain, it might change from species to species. How kisspeptin is regulated was quite ambiguous, but recent studies show that estrogen, Neuropeptide Y, Pro-opio melanocortin

(POMC), Agouti-related protein (AgRP) and Leptin are the major regulators of kisspeptin expression. (Amstalden et al., 2014; Goto et al., 2015; Korner et al., 2001; Padilla et al., 2017). Other than these regulators certain transcription factors also regulate the expression of Kisspeptin, Cdx1, Sp1, Est1, Gata1, Gata2, and Sry were known to be binding the promoter region of KISS1 gene (within the arcuate nucleus) (Goto et al., 2015). In study conducted by (Tomikawa et al., 2012) showed that transcriptional factors which lead to the histone acetylation of the ARC KISS1 gene promoter upregulated the expression of Kisspeptin.

## II. REGULATION OF PUBERTY BY miRNA

Pubertal onset as previously described is affected by many factors, one such factor is miRNA.

miRNA are short non-coding RNAs, they regulate at the post-transcriptional level by repressing the gene expression. miRNA have lately been emerged as major regulators of this complex developmental process. (Messina et al., 2016; Sangiao-Alvarellos et al., 2013). Different studies have found the role of various miRNA in the onset or delay of puberty.

miRNA	Role	Reference
Let-7a	Supressed by Lin28B	(Sangiao-Alvarellos et al., 2013)
miR-200 and miR-155	Increased expression in GnRH neurons during infantile period leads to inhibition of ZEB1 and Cebpb (GnRH supressing factors).	(Messina et al., 2016)
miR30-b	Supress Mkrn3 (a pubertal inhibitory factor), thus promotes pubertal onset.	(Heras et al., 2019)
miR-7a2	Deletion of miR-7a2 leads to hypogonadotropic hypogonadism and infertility.	(Ahmed et al., 2017)
miR-382-3p	Declining levels leads to onset of spermatogenesis	(Gupta et al., 2021)

## III. DISORDERS OF PUBERTY

(Klein et al., 2017) defines precocious puberty as pubertal onset before 8 years of age in girls and before nine years of age in boys. Body undergoes a lot of physiological and develops secondary sexual characteristics during the phase of puberty. (Iyare et al., 2010) reports that neonatal mice that were undernourished during the lactation phase developed delayed pubertal onset. Delayed puberty is usually self-limited and hardly because of familial factors like genetic factors. One of the major factors that might lead to abnormal pubertal onset in females is Anorexia.(Klump, 2013).

## IV. CURRENT DETECTION OF PUBERTAL ONSET

Physical examination via observation of growth of genitalia (male) and enlargement of breasts (different stages) in girls. There is a need of other detection techniques that inform

about precocious puberty or delayed puberty, identification of markers that lead to up/down regulation of the genes involved in pubertal onset (Rzeczowska et al., 2014). Next-generation sequencing and genome wide association approaches are helping rapid expansion of gene discovery in delayed puberty (Howard & Dunkel, 2019). Early detection in the alteration of Kisspeptin and/or GnRH levels can also serve as markers for pubertal onset, other than these factors changes in expression patterns of transcriptional factors identified by CHIP assay can also serve as markers for pubertal onset (Mancini et al., 2019). As there are very less cases of genetic/ familial conditions leading to delayed/precocious puberty it is difficult to generate a common detection tool for the same (Sørensen et al., 2012).

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