

Genetic and Epigenetic Control of Puberty

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Abstract

Puberty is a complex transitional phase in which reproductive capacity is achieved. There is a very wide variation in the age range of the onset of puberty, which follows a familial, ethnic, and sex pattern. The hypothalamic-pituitary-gonadal axis and several genetic, environmental, and nutritional factors play an important role in the onset of and throughout puberty. Recently, there has been significant progress in identifying factors that affect normal pubertal timing. Different studies have identified single nucleotide polymorphisms (SNPs) that affect pubertal timing in both sexes and across ethnic groups. Single genes are implicated in both precocious and delayed puberty, and epigenetic mechanisms have been suggested to affect the development and function of the GnRH neuronal network and responsiveness of end organs. All these factors can influence normal puberty timing, precocious puberty, and delayed puberty. The objec-

tive of this review is to describe recent findings related to the genetic and epigenetic control of puberty and highlight the need to deepen the knowledge of the regulatory mechanisms of this process in the normal and abnormal context.

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Introduction

Puberty is an important period of growth and psychological and physical development in which reproductive capacity is achieved [Temboury Molina, 2009; Zhu et al., 2018]. It begins with the appearance of secondary sexual characteristics. This is followed by a sequence of maturation changes resulting from increased production of gonadal sexual steroids in response to increased secretion of gonadotropins (LH: luteinizing hormone and FSH: follicle-stimulating hormone) by the anterior pituitary gland [Mustanski et al., 2004]. There is a very wide variation in the age range of the onset of puberty, which follows a familial, ethnic, and sex pattern [Temboury Molina, 2009]. Although the factors that explain individual differences in pubertal timing have not been fully identified, evidence

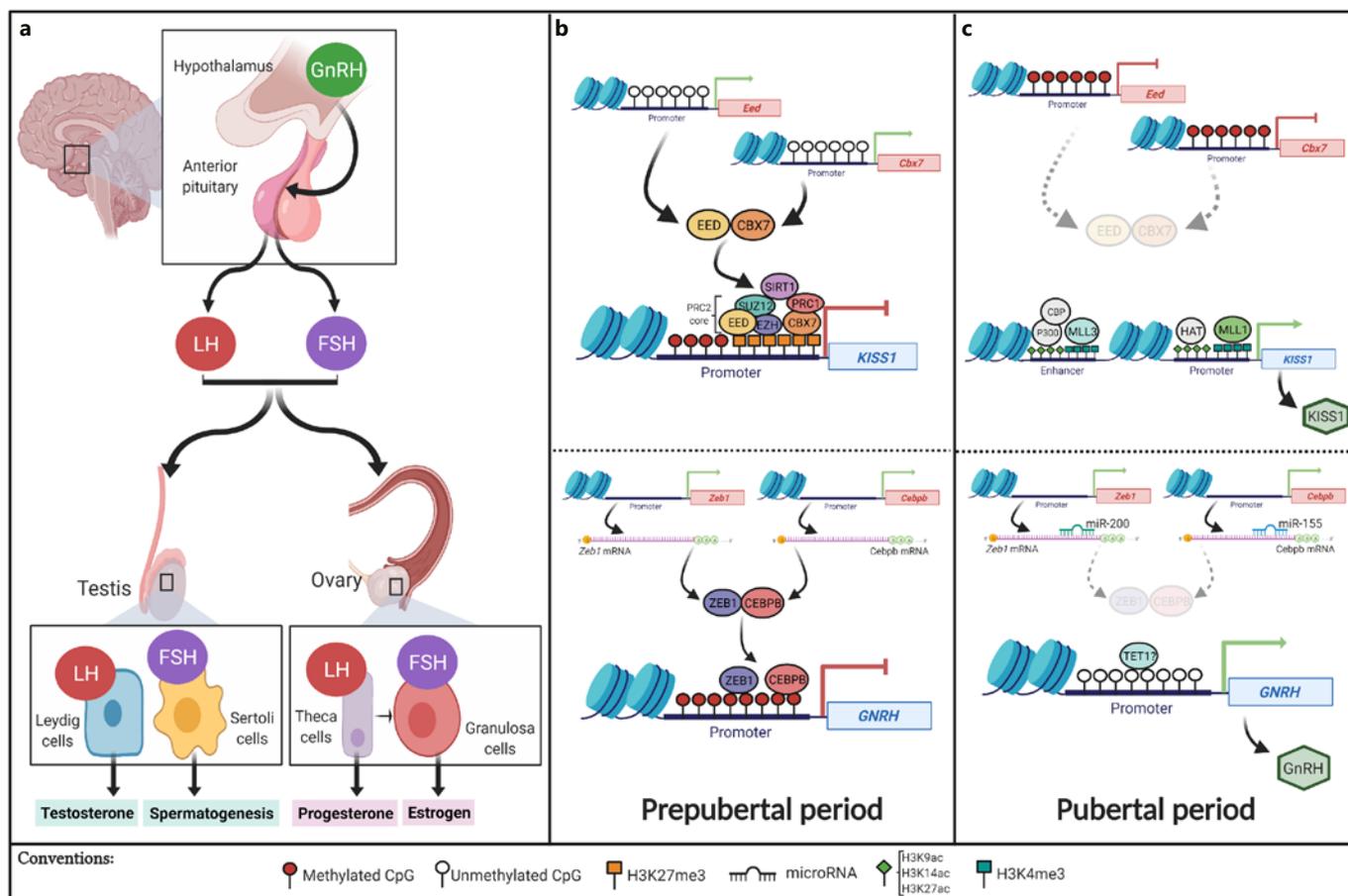


Fig. 1. Epigenetic control of the HPG axis during pubertal development. **a** Schematic representation of the HPG axis. The main organs and hormones involved and their role in pubertal development are shown. **b** Epigenetic control of genes of the HPG axis that mediate their repression in the prepubertal period are summarized and schematized. **c** Activation of these genes during the subsequent pubertal period (created in Biorender).

shows that the GnRH neuronal network acts under genetic control and environmental influence [Mustanski et al., 2004; Tembory Molina, 2009]. In this regard, it is proposed that there is a change in the gene expression of activators and inhibitors of puberty during the pubertal transition where the epigenetic machinery controls this genetic balance [Toro et al., 2018]. The purpose of this review is to describe recent findings related to the genetic and epigenetic control of puberty.

The Hypothalamic-Pituitary-Gonadal Axis

To attain sexual competence, all mammalian species go through puberty, a maturational period during which body growth and development of secondary sexual characteristics occur. Control of reproductive functions in

humans requires temporal regulation from the hypothalamic-pituitary-gonadal (HPG) axis [Ojeda and Terasawa, 2002; López, 2012; Aylwin et al., 2019a].

This hormonal axis plays a major role during puberty, which begins with the diurnal and pulsatile secretion of gonadotropin-releasing hormone (GnRH) for a prolonged period. This release occurs in response to excitatory impulses mainly from the secretory neurons of the hypothalamic arcuate nucleus [Jones and Lopez, 2013; Lomniczi et al., 2015]. In response to GnRH, the anterior pituitary stimulates an increase in the pulsatile release of LH, which is initially released nocturnally, and FSH. The latter, in turn, induces the synthesis of steroid hormones in the gonad (Fig. 1a).

In the male gonad, LH acts directly on Leydig cells, inducing the synthesis of testosterone from cholesterol. On the other hand, FSH induces the initiation of spermatogenesis.

genesis in Sertoli cells. In the female gonad, LH stimulates the production of progesterone in theca cells, while FSH induces an increase in estrogen synthesis from granulosa cells (Fig. 1a) [López, 2012]. The increase in these steroid hormones in the gonad is responsible for the correct development of primary and secondary sexual characteristics [López, 2012; Lomniczi et al., 2015].

Although the pubertal process is known to have a strong genetic component, in recent years, epigenetics has been implicated as a significant regulatory mechanism that controls GnRH release. In this way, the expression of GnRH is repressed for the first time before puberty and is activated later; this produces an increase in the secretion of gonadotropins, which coincides with the beginning of the pubertal process [Ojeda and Terasawa, 2002; Aylwin et al., 2019b].

Genetic Control of Normal Pubertal Development

Pubertal development is estimated to be 50–75% heritable [Grotzinger et al., 2018; Zhu et al., 2018]. There is evidence of a positive correlation between the onset of puberty, the pubertal stage, and the levels of testosterone, DHEA (dehydroepiandrosterone), and progesterone among monozygotic and dizygotic twins, which supports the theory of genetic control in pubertal development [Grotzinger et al., 2018]. Furthermore, in recent years, epigenetics has been recognized as a regulatory mechanism that controls GnRH release before puberty and then modulates the increase in GnRH secretion to initiate the pubertal process [Toro et al., 2018].

During the prepubertal period, the secretory activity of GnRH neurons is predominately under inhibitory control, and for the onset of puberty, the central restriction must be lost. It is generally accepted that a decrease in inhibitory signals, along with an increase in excitatory neurotransmission, is required to initiate the pubertal process. Recent evidence shows that this intercellular mechanism of excitatory/inhibitory balance is a reflex of gene expression [Lomniczi et al., 2015; Toro et al., 2018]. In this regard, 3 groups of genes have been proposed: (1) puberty inhibitor (PI) genes: *GAD67*, *PDYN*, and *GnIH*; (2) puberty-activating (PA) genes: *GnRH*, *GLS*, *KISS1*, and *TTF1*; and (3) genes with a dual effect, according to the hormonal environment and cell identity: *TAC3* and *EAPI* [Toro et al., 2018].

Evidence for pubertal control of most of the genes mentioned above comes from animal models and/or the construction of gene coexpression networks with the help

of bioinformatics tools [Toro et al., 2018]. Of this group of genes, the *KISS1* gene should be highlighted. This gene encodes kisspeptin, which binds to the KISSR receptor on GnRH neurons to activate the pulsatile secretion of GnRH and promote the onset of puberty [Lomniczi et al., 2015]. The expression of *KISS1* occurs in 2 main populations of neurons: kisspeptin neurons and kisspeptin/neurokinin B/dynorphin (KNDy) neurons. Positive regulation of *KISS1* expression in KNDy neurons is mediated by the binding of sex steroids to their receptors ER α and PR. The other way is by binding of neurokinin B and dynorphin to neurokinin B receptor and kappa-opioid peptide receptor [Skorupskaite et al., 2014; Livadas and Chrousos, 2016; Marques et al., 2018; Yeo and Colledge, 2018]. This ensures the expression of *KISS1* for proper pubertal development.

Epigenetic Control of Puberty

Although puberty has a strong genetic determination, the establishment of puberty is highly sensitive to endogenous and exogenous signals dependent on environmental factors, such as diet, nutritional status, exposure to endocrine disruptors, stress, and arduous physical training, that can affect the functionality of the HPG axis with consequences on reproductive capacity [Motti and Meccariello, 2019]. It is known that states of malnutrition, such as undernutrition and overnutrition, are causes of delayed and precocious puberty, respectively. It is now recognized that puberty is finely controlled by epigenetic mechanisms [Vazquez et al., 2018]. Epigenetics is the science that studies heritable changes in gene expression without altering the DNA sequence. Currently, 5 epigenetic mechanisms are recognized: DNA methylation, covalent histone modification (CHM), histone variants, chromatin remodeling complexes, and noncoding RNAs [Bártová et al., 2008; Kim et al., 2009; Toro et al., 2018]. Through epigenetic regulation, all genes in an organism are expressed in an orderly fashion at a specific time and in a specific tissue, including those involved in the proper functioning of the HPG axis [Lomniczi et al., 2015].

During the prepubertal period, in the hypothalamus, the expression of puberty-activating genes is repressed. Such is the case with the *KISS1* gene that encodes kisspeptin, which is a major actor in the HPG axis that initiates puberty through GnRH release. The expression of the *KISS1* gene is repressed by methylation in the CpG islands of its promoter region and the addition of H3K-27me₃, which is a repressive histone mark, and this is

Table 1. Enzymes involved in the epigenetic control of pubertal development

Gene target	Stage of puberty	Regulator enzyme	Enzyme function	Associated epigenetic mark	Effect
PcG (Cbx7 and Eed promoters)	Pubertal	DNMT	Writer	CpG methylation	Activation of <i>Kiss1</i>
<i>Kiss1</i> promoter	Prepubertal	PcG (Eed and Cbx7)	Writer	H3K27me3	Repression of <i>Kiss1</i>
		GATAD1	Reader	H3K4me2	
<i>Kiss1</i> promoter	Pubertal	KDM1	Eraser	H3K4me2	Activation of <i>Kiss1</i>
		SIRT1	Eraser	H3K9ac, H3K14ac, H3K56ac and H4K16ac	
		MLL1	Writer	H3K4me3	
		HAT	Writer	H3K9ac and H3K14ac	
<i>Kiss1</i> enhancer	Pubertal	MLL3	Writer	H3K4me3	Activation of <i>Kiss1</i>
		P300/CBP	Writer	H3K27ac	
Zeb1/GnRH and Cebpb	Pubertal	DICER	miRNA processing	miR-200 and miR-155	Activation of GnRH
GnRH	Prepubertal	DNMT	Writer	CpG methylation	Repression of GnRH

The target genes of epigenetic regulation during pubertal development, the main responsible epigenetic enzymes, their function, the associated epigenetic mark, and their effect on pubertal development that have been described to date. Adapted and modified from Toro et al. [2018] and Vazquez et al. [2018].

catalyzed by the enzymes of the Polycomb group (PcG): EED (Embryonic Ectoderm Development) and CBX7 (Chromobox protein homolog 7) [Kouzarides, 2007; Lomniczi et al., 2013; Toro et al., 2018]. Also interacting with PcG proteins is the SIRT1 (Sirtuin Type 1) enzyme, which removes histone acetylation, thus reinforcing the repressor effect on *KISS1* [Vazquez et al., 2018]. Additionally, the expression of *KISS1* is repressed by the action of the GATAD1 and KDM1 (histone demethylase) enzymes, which identify and remove the activating H3K4me2 mark, respectively [Toro et al., 2018; Motti and Meccariello, 2019]. Moreover, the binding of the transcriptional repressors *Zeb1* and *Cebpb* has been evidenced in a murine model (Fig. 1b) [Toro et al., 2018].

For the transition to puberty, the genes that activate this process must change their regulatory regions to a state of activation. For *KISS1*, the event starts with the eviction of the repressor enzymes EED, CBX7, and SIRT1 from the *KISS1* promoter, and then, there is a progressive enrichment of the activator mark H3K4me3 mediated by the concomitant recruitment of MLL1 and MLL3 (mixed lineage leukemia). Other activating enzymes, such as HAT and P300/CBP, are also involved in this activation process, and they catalyze the addition of acetylations, such as H3K9ac, H3K14ac, and H3K27ac, in both the promoter and enhancer region of *KISS1* to facilitate their expression (Table 1) [Lomniczi et al., 2013; Toro et al., 2018]. As the pubertal period approaches, there is a DNA

demethylation process in the *GNRH* promoter, thus facilitating its expression (Fig. 1c) [Kurian et al., 2010; Livadas and Chrousos, 2019]. It is believed that this demethylation is mediated by Tet enzymes because they are overexpressed during neuronal maturation, and there is evidence in murine models that indicates that the absence of Tet1 results in deficits in reproductive capacity [Kurian et al., 2010; Kurian and Terasawa, 2013].

Positive regulation of *GNRH* transcription by a network of miRNAs has also been observed. In a murine model, it has been shown that the microRNAs miR-200 and miR-155 regulate *Gnrh1* expression through post-transcriptional control of *Zeb-1* and *Cebpb* expression, which in turn act as transcriptional repressors of *Gnrh1* (Fig. 1c) [Messina et al., 2016]. Another miRNA with a potential effect on puberty is miR-7a2, which is believed to be essential for normal murine pituitary development and HPG axis function; its deletion in mice leads to hypogonadotropic infertility [Howard and Dunkel, 2018; Toro et al., 2018].

The enzymes of PcG and TrxG groups are critical regulators of many developmental genes. They act in an antagonistic way since the proteins of the PcG group catalyze repression by adding the repressor marks H3K27Me3 and H2AK119Ub. On the other hand, the proteins of the TrxG group activate gene expression by adding the activating marks H3K4Me, H3K4Me2, and H3K4Me3 to the regulatory regions of the gene [Schuettengruber et al., 2007; Lomniczi et al., 2015]. The removal of the EED and

CBX enzymes of the PcG family at the beginning of pubertal development is a consequence of the methylation of their promoters and the decrease in the gene expression of these enzymes, a phenomenon that precedes pubertal development (Fig. 1c) [Lomniczi et al., 2013; Aylwin et al., 2019a; Livadas and Chrousos, 2019]. Additionally, it has been observed that the elimination of the EED and SIRT1 repressor enzymes from the *KISS1* promoter for the onset of puberty is accelerated or delayed depending on the nutritional status, causing early or delayed puberty [Lomniczi et al., 2013].

Just as *GNRH* and *KISS1* genes have a key role in the regulation of pubertal development, undoubtedly, the genes encoding their receptors, downstream genes of the HPG axis, such as *LHB*, *FSHB*, and those involved in steroidogenesis in the gonad are potential targets for epigenetic regulation. However, to date, the epigenetic regulation of these genes at puberty has not been characterized. Furthermore, it has been shown that the FSH receptor (FSHR) and the genes *CYP11A1*, *HSD3B1*, *CYP17A1*, and *CYP19A1* are involved in steroidogenesis and are susceptible to control by DNA methylation [Zhang and Ho, 2011].

Genetics of Normal Female Puberty

Puberty is considered normal when it begins between the ages of 8 and 13 in females [Abreu and Kaiser, 2016], with the appearance of the breast bud being the first sign of the onset of puberty. To explain what contributes to the onset of puberty at a molecular level, Hagen et al. [2014] evaluated the effect of 3 polymorphisms that influence the action of FSH on the age at thelarche in a cohort of 964 healthy girls. In this study, girls homozygous for the *FSHR*-29AA (c.-29G>A) variant, located in the gene-promoting region, were found to enter puberty 7.4 (2.5-12.4) months later than carriers of the common *FSHR*-29GG+GA variants ($p = 0.003$). It seems that the *FSHR* c.-29G>A variant reduces the expression of the FSHR receptor [Hagen et al., 2014]. Additionally, it was reported that the *FSHB* -211TT (c.-211G>T) variant, which is located in the promoter of the gene encoding the FSH β subunit, produces a decrease in FSH production due to an alteration in the affinity of the LHX3 transcription factor for the *FSHB* gene promoter [Benson et al., 2013]. This occurs when it is present in a homozygous state, and compared to carriers of the *FSHB*-211GG and GT variants, it facilitates a later onset of puberty, although it is not statistically significant. However, it has an additive effect in

increasing the age of puberty onset up to 1.9 (0.2-3.6) months when found concomitantly with the *FSHR* c.-29G>A variant [Benson et al., 2013].

Moreover, variants in the *LIN28B* gene, a powerful and specific regulator of microRNA processing [Ong et al., 2009], have also been involved in modifying the timing of thelarche. The *LIN28B* variant g.105378954C>T (rs7759938) in the homozygous state was associated with the onset of thelarche 8.06 months later compared to carriers of the common variant, whose effect was independent of the variants described above [Busch et al., 2018]. Furthermore, there is evidence that rs7759938 in the homozygous state is associated with the onset of menarche 6.02 months later compared to carriers of the common variant [Busch et al., 2018]. In another large genome-wide association (GWA) study, it was observed that the *LIN28B* rs314276 polymorphism was associated with an earlier mean age at menarche by 0.22 years (95% CI = 0.14–0.29) [Ong et al., 2009].

Another variant of interest for its effect on the action of FSH is the *FSHR* variant c.2039A>G; pN680S, which is located in the gene region encoding the intracellular domain of the FSH receptor. It has been observed that homozygous carriers of this variant need more exogenous FSH for sufficient ovarian stimulation compared to homozygous carriers for the *FSHR* 2039AA variant or composite heterozygous *FSHR* 2039AG [Perez Mayorga et al., 2000]. Although this variant does not appear to influence puberty onset [Hagen et al., 2014], carriers of the *FSHR* 2039GG genotype have been observed to have significantly smaller glandular breast tissue and lower serum estradiol concentrations [Ong et al., 2009; Henriksen et al., 2016; Busch et al., 2018].

It is also important to point out that the beginning of puberty is a highly polygenic process and that rare variants near the *MKRN3* and *DLK1* genes, when inherited by the paternal line, have been associated with early puberty and precocious puberty [Perry et al., 2014; Pagani et al., 2020]. The association of these genes with precocious puberty is detailed in the section on the genetics of precocious puberty.

Genetics of Normal Male Puberty

Puberty in males is considered normal when it begins between 9 and 14 years of age [Abreu and Kaiser, 2016]. The onset and progression of puberty in boys are manifested by gradual enlargement of the external genitalia, initially of the testicular volume, and the extension of

the pubic hair. By convention, these characteristics are classified into 5 stages of sexual maturation. However, it is difficult to assess these stages accurately in retrospective epidemiological studies. Voice change represents a distinctive event that usually occurs abruptly at the end of puberty and is taken as a marker of pubertal development [Ong et al., 2009; Day et al., 2015]. It has been observed that the *LIN28B* rs314276 polymorphism is associated with a voice change at the age of 15, an advanced stage of pubic hair at the age of 13 (described as Tanner 5), and an accelerated growth rate at age 10 [Ong et al., 2009].

Genetics of Precocious Puberty

Precocious puberty is defined clinically by the development of secondary sexual characteristics before the age of 8 years in girls and 9 years in boys [Yi et al., 2018]. It is associated with a low final height, compared to their genetic potential for height, and an increased risk of developing psychological problems [Wojniusz et al., 2016; Yi et al., 2018], which may be gonadotropin-dependent or gonadotropin-independent [Teles et al., 2008].

Gonadotropin-Dependent Precocious Puberty or Central Precocious Puberty

Central precocious puberty (CPP) is caused by the early maturation of the HPG axis [Abreu and Kaiser, 2016]. In 2008, the first monogenic cause of CPP was identified in a patient with a heterozygous gain-of-function mutation in the *KISS1R* gene, which codes for the kisspeptin receptor [Teles et al., 2008; Canton et al., 2019]. In 2010, a mutation in the *KISS1* gene was described in a child who developed CPP at 1 year of age [Silveira et al., 2010]. Recently, pathogenic variants in the *MKRN3* gene have been associated with cases of familial and nonfamilial CPP [Abreu et al., 2013; Schreiner et al., 2014; Yi et al., 2018]. *MKRN3* plays a role in protein ubiquitination and can act by inhibiting factors that stimulate pulsatile pubertal GnRH release [Schreiner et al., 2014]. Mutations causing loss of *MKRN3* function are claimed to represent the most common genetic cause of nonsyndromic CPP [Valadares et al., 2019]. Recently, mutations causing loss of function in the *DLK1* gene have been described in women with a history of precocious puberty and metabolic disorders, such as overweight/obesity, glucose intolerance/type 2 diabetes mellitus, and hyperlipidemia [Dauber et al., 2017; Canton et al., 2019; Gomes et al., 2019] (Table 2).

On the other hand, CPP is part of the phenotypic spectrum of some chromosome diseases, including Temple syndrome (associated with the involvement of the chromosomal region susceptible to imprinting and involving the *DLK1* gene), Silver-Russell syndrome, and Williams-Beuren syndrome [Macedo et al., 2016; Canton et al., 2019]. Additionally, there are some polymorphic variants in the *GNRH1*, *LHB*, *FSHB*, *TTF1*, *EAP1*, *NPVF*, and *NPFFR1* genes (which are biologically linked to gonadotropin signaling) and the *CYP19A1*, *CYP11A1*, *CYP17*, and *CYP11B1* genes (genes encoding steroidogenesis enzymes) with possible associations with precocious puberty. However, the small size of the studies excludes any definitive conclusions [Zhu et al., 2018]. In addition, some variants in copy numbers, such as 1p36 deletion, 9p distal deletion, 9q34.3 duplication (which includes the *NOTCH* gene), Xp11.23p11.22 duplication, and *CDKL5* gene deletion, have been associated with idiopathic CPP [Canton et al., 2019] (Table 2).

Gonadotropin-Independent Precocious Puberty or Peripheral Precocious Puberty

Genetic causes of autonomic gonadal activation have been widely described, such as testotoxicosis and McCune-Albright syndrome (MAS) [Macedo et al., 2016] (Table 2).

Testotoxicosis, or familial precocious puberty limited to the male, is caused by germline mutations with constitutive activation of the *LHCGR* gene, which encodes the luteinizing hormone receptor/choriogonadotropin receptor located on chromosome 2p21. The inheritance pattern is autosomal dominant. Pituitary LH and placental human chorionic gonadotropin bind with high affinity to LHCGR. Activating mutations in *LHCGR* lead to increased production of cAMP and testosterone in the absence of LH. Family members with the same mutation may present phenotypes of variable severity, suggesting variable expression of the disease [Macedo et al., 2016] (Table 2).

MAS is caused by postzygotic somatic activating mutations in the *GNAS* gene, which encodes the α subunit of the guanine nucleotide-binding protein (G α) that stimulates adenylate cyclase and leads to the generation of cAMP. Clinically, this disorder is characterized by a classic triad of café-au-lait skin pigmentation areas, polyostotic fibrous dysplasia, and peripheral precocious puberty. The clinical presentation is heterogeneous and may include other hyperfunctional endocrinopathies [Macedo et al., 2016] (Table 2).

Table 2. Genetic causes of puberty disorders

Category	Genetic causes
Precocious puberty	
Central precocious puberty	<p>Monogenic causes:</p> <ol style="list-style-type: none"> (1) Gain-of-function (activating) mutations in <i>KISS1R</i> and <i>KISS1</i> genes (kisspeptin pathway genes) (2) Loss-of-function (inactivating) mutations in <i>MKRN3</i> gene (3) Loss-of-function (inactivating) mutations in <i>DLK1</i> gene <p>Chromosomal abnormalities:</p> <ol style="list-style-type: none"> (1) 1p36 deletion (2) 9p distal deletion (3) 9q34.3 duplication (which includes the NOTCH gene) (4) Xp11.23-p11.22 duplication
Peripheral precocious puberty	<ol style="list-style-type: none"> (1) Testotoxicosis: constitutive activation germline mutations in the <i>LHCGR</i> gene (2) McCune Albright syndrome: postzygous somatic activating mutations in <i>GNAS</i>
Genetics of delayed puberty	
Constitutional delay of growth and puberty	Genetic background is unknown. Probably pathogenic variants in the <i>IGSF10</i> gene have been associated
Kallmann syndrome	Mutated genes: <i>KAL1</i> , <i>FGFR1</i> , <i>FGF8</i> , <i>FGF17</i> , <i>IL17RD</i> , <i>DUSP6</i> , <i>SPRY4</i> , <i>FLRT3</i> , <i>KLB</i> , <i>HS6ST1</i> , <i>CHD7</i> , <i>WDR11</i> , <i>SEMA3A</i> , <i>SEMA3E</i> , <i>IGSF10</i> , <i>SMCHD1</i> , <i>CCDC141</i> , <i>FEZF1</i> , <i>SOX10</i> , <i>PROKR2</i> , <i>PROK2</i>
Normosmic idiopathic hypogonadotropic hypogonadism	Mutated genes: <i>CHD7</i> , <i>DAX1</i> , <i>FGF8</i> , <i>FGF17</i> , <i>FGFR1</i> , <i>HS6ST1</i> , <i>NSMF</i> , <i>LEP</i> , <i>LEPR</i> , <i>PROK2</i> , <i>PROKR2</i> , <i>WDR11</i> , <i>GNRH1</i> , <i>GNRHR</i> , <i>KISS1</i> , <i>KISS1R</i> , <i>SRA1</i> , <i>TAC3</i> , <i>TACR3</i>
Hypogonadism hypergonadotropic	<p>Monogenic causes:</p> <ol style="list-style-type: none"> (1) Enzymatic defects in testosterone biosynthesis: 17α-hydroxylase, 3β-hydroxysteroid dehydrogenase, 17, 20-lyase and 17β-hydroxysteroid dehydrogenase deficiency (2) Inactivating mutations in the gonadotropin receptor genes (3) Polymalformative syndromes <p>Chromosomal abnormalities:</p> <ol style="list-style-type: none"> (1) Turner syndrome (2) Klinefelter syndrome

Genetics of Delayed Puberty

Delayed puberty is clinically defined by the absence or incomplete development of secondary sexual characteristics after age 13 in girls or after age 14 in boys [Abreu and Kaiser, 2016; Raivio and Miettinen, 2019]. Delayed puberty may be a variant of normal development, known as constitutional delay of growth and puberty, where the onset of puberty is delayed but occurs spontaneously before age 18. In contrast, hypogonadism is characterized by the absence or incomplete development of secondary sexual characteristics at age 18 in both sexes. Hypogonadism can be hypogonadotropic or hypergonadotropic [Abreu and Kaiser, 2016; Zhu et al., 2018] (Table 2).

Constitutional Delay of Growth and Puberty

Constitutional delay of growth and puberty (CDGP) is predominantly segregated in an autosomal dominant pattern of inheritance. However, its genetic background is unknown. Potentially pathogenic variants in the *IGSF10* gene have been associated with CDGP [Howard et al.,

2016]. Studies in mouse and zebrafish models suggest that *IGSF10* is required for proper migration of GnRH neurons [Howard et al., 2016]. Rare variants have also been associated with the *GHSR* gene (which encodes the ghrelin receptor) and the *LEP* gene (which encodes leptin). However, it is not clear whether these variants are more common in individuals with delayed puberty than in the general population [Zhu et al., 2018] (Table 2).

Hypogonadotropic Hypogonadism

This disorder can be caused by a deficiency in GnRH secretion or action or both, and it can be classified as idiopathic or secondary. Idiopathic hypogonadotropic hypogonadism (IHH) is divided into 2 major categories: Kallmann syndrome (KS) and normosmic IHH (nIHH). Inactivating variants in more than 50 genes have been reported to cause IHH. These genetic defects have been identified in approximately 40–50% of cases [Abreu and Kaiser, 2016; Topaloglu, 2017].

KS is associated with anosmia or isolated hypogonadotropic hypogonadism when the sense of smell is not

compromised [Abreu and Kaiser, 2016]. It is caused by a defect in the development of the olfactory system and by embryonic migration interruption of GnRH-synthesizing neurons from the olfactory epithelium to the hypothalamic region of the brain. Most known cases are sporadic, but familial forms have been described. Some causative genes include *KAL1* in the X-linked form; *FGFR*, *FGF8*, *CHD7*, and *SOX10* in the AD form; and *PROKR2* and *PROK2* in the AR form [Balasubramanian and Crowley, 2017]. Normosmic IHH results from dysfunction of normally placed GnRH neurons in the hypothalamus. These cases typically do not have any accompanying congenital lesions, and pathogenic variants in the *CHD7*, *FGF8*, *FGF17*, *FGFR1*, *HS6ST1*, *NSMF*, *PROK2*, *PROKR2*, *WDR11*, *GNRH1*, *GNRHR*, *KISS1*, *KISS1R*, *TAC3*, and *TACR3* genes have been described to cause nIHH [Balasubramanian and Crowley, 2017] (Table 2).

Hypergonadotropic Hypogonadism

Gonadal failure is a relatively common cause of delayed puberty in girls (21%), but it is rarely found in boys (4%). Regarding hypergonadotropic hypogonadism in girls, approximately one-quarter of cases are attributed to Turner syndrome [Raivio and Miettinen, 2019]; other causes include pure gonadal dysgenesis and loss-of-function mutations in the genes encoding gonadotropin receptors [Mayáyo et al., 2010]. Klinefelter syndrome is the most common cause of male hypogonadotropic hypogonadism. Similarly, enzymatic defects in testosterone biosynthesis, such as 17 α -hydroxylase, 3 β -hydroxysteroid dehydrogenase, 17,20-lyase, and 17 β -hydroxysteroid dehydrogenase deficiencies, and inactivating mutations in gonadotropin receptor genes have also been associated with hypergonadotropic hypogonadism in boys [Mayáyo et al., 2010]. It should be noted that several polymalformative syndromes are accompanied by hypogonadotropic hypogonadism. Among these, Noonan syndrome stands out as one of the main syndromes associated with hypogonadotropic hypogonadism in both girls and boys [Mayáyo et al., 2010] (Table 2).

Conclusion

Puberty is a period of growth and psychological and physical development in which reproductive capacity is achieved. It begins with the appearance of secondary sexual characteristics followed by a sequence of changes. The changes result from the increased production of gonadal

sex steroids in response to increased secretion of gonadotropins by the anterior pituitary gland, which is driven by the hypothalamic release of GnRH. In this process, the GnRH neuronal network acts under genetic and epigenetic control and environmental influence. The beginning of puberty is a highly polygenic process. In this regard, 3 groups of genes have been proposed: puberty inhibitor genes, puberty-activating genes, and genes with a dual effect. Of this group of genes, *KISS1* gene encodes kisspeptin, which is a major actor in the HPG axis that initiates puberty through GnRH release. The expression of the *KISS1* gene is repressed by methylation in the CpG islands of its promoter region, and this is catalyzed by the enzymes of the Polycomb group and the action of the GATAD1 and KDM1 enzymes. GnRH also have a key role in the regulation of pubertal development. Undoubtedly, the genes encoding their receptors, downstream genes of the HPG axis, such as *LHB*, *FSHB*, and those involved in steroidogenesis in the gonad are potential targets for epigenetic regulation. However, to date, the epigenetic regulation of these genes at puberty has not been characterized.

Rare variants in *MKRN3*, *DLK1*, *KISS1*, and *KISS1R* genes represent the known genetic causes of CPP. There are some polymorphic variants in the genes with are biologically linked to gonadotropin and genes encoding steroidogenesis enzymes with possible associations with precocious puberty. In addition, some variants in copy numbers have been also associated, however, the small size of the studies excludes any definitive conclusions.

CDGP is predominantly segregated in an autosomal dominant pattern of inheritance, however, its genetic background is unknown. Potential pathogenic variants in the *IGSF10* gene and variants in *GSHR* and *LEP* genes have been associated, however, it is not clear whether these variants are more common in individuals with delayed puberty than in the general population. In relation to delayed puberty associated to hypogonadotropic hypogonadism, the genetic defects have been identified in approximately 40–50% of cases. On the other hand, gonadal failure is a relatively common cause of delayed puberty in girls, but it is rarely found in boys.

The timing and progression of puberty depend on the strict control of the genetic and epigenetic machinery and different internal and external environmental stimuli. Undoubtedly, there is much to discover and understand about the signaling pathways triggered by genetic and epigenetic mechanisms responsible for prepubertal neuroendocrine development.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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