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Delayed and Precocious Puberty – Genetic Underpinnings and Treatments

Anisha Gohil, D.O. [Pediatric Endocrinology Fellow],
Division of Pediatric Endocrinology, Department of Pediatrics, Riley Hospital for Children at IU Health, Indiana University School of Medicine, 705 Riley Hospital Drive, Room 5960, Indianapolis, IN 46202

Erica A. Eugster, M.D. [Professor of Pediatrics]
Division of Pediatric Endocrinology, Department of Pediatrics, Riley Hospital for Children at IU Health, Indiana University School of Medicine, 705 Riley Hospital Drive, Room 5960, Indianapolis, IN 46202

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Introduction

Great variability in timing of pubertal onset exists, with both genetic and environmental factors playing a role [1]. However, genetics is the main contributor with 50–80% influence over determination of pubertal timing [1]. This is particularly true for menarche, with approximately half of the variation in timing being from genetic factors [2]. Important insights into the critical role of genetics have been revealed from twin studies which have demonstrated that monozygotic compared to dizygotic twins have greater concordance in pubertal timing [1]. In the last decade, large genome-wide association studies have identified multiple loci responsible for the timing of menarche [3,4]. Although these loci explain only a small percentage of the variance and heritability of pubertal timing, they have revealed that it is highly polygenic [3,4]. The many single gene disorders contributing to either delayed or precocious puberty also demonstrate the significant and highly complex role of genes in the regulation of puberty [1].

This review describes the main genetic causes of delayed puberty (hypogonadotropic and hypergonadotropic) and precocious puberty (central and peripheral), as well as the available treatment options for these conditions. The full-length phrasing of acronyms for gene mutations found in this review are listed in Table 1.

Corresponding author agohil@iu.edu, Phone 317-944-3889, Fax 317-944-3882.

Content

Constitutional Delayed Puberty

Constitutional delay of growth and puberty is a variation of normal development in which puberty occurs at or later than the upper end of the normal range [5]. Puberty is considered delayed when there is a lack of breast development in a girl by age 13 and lack of testicular enlargement to 4 mL or more in a boy by age 14. The majority of delayed puberty is self-limited with two-thirds of patients having constitutional delay [6]. There is often a family history of delayed puberty. Interestingly, individuals with constitutional delay have been found to have significantly higher rates of pathogenic variants compared to unaffected family members or controls, particularly in the genes *TAC3* and *IL17RD*, the latter thought to have a role in fate specification of gonadotropin-releasing hormone (GnRH) neurons [7].

Hypogonadotropic Hypogonadism

Hypogonadotropic hypogonadism (HH) is caused by abnormalities within the hypothalamus or pituitary and is characterized by low gonadotropin and sex steroid levels. Etiologies of HH can be congenital or acquired [5]. This review focuses on congenital forms including gene mutations and syndromes.

Kallmann Syndrome—Isolated hypogonadotropic hypogonadism (IHH) without other pituitary hormone deficiencies can occur with or without anosmia. With anosmia, the condition is called Kallmann syndrome [8]. During normal embryological development, GnRH secreting neurons originate in the olfactory placode and migrate to the hypothalamus [9]. Certain mutations disrupt the interconnected olfactory and GnRH neuronal migration process, leading to Kallmann syndrome [8].

About 60% of individuals with IHH have anosmia (Kallmann syndrome) [10]. Fifteen percent of cases are caused by a mutation in *ANOS1* (also known as *KAL1*) or *FGFR1* [10]. The *ANOS1* gene encodes for the neural cell adhesion protein molecule anosmin-1, which is essential for normal neuronal migration during early development [10]. *ANOS1* mutations are X-linked recessive and associated findings include unilateral renal agenesis and bimanual synkinesis [8]. *FGFR1* mutations demonstrate autosomal dominant transmission and can be associated with cleft palate, dental agenesis, or skeletal anomalies [8]. An additional 5–10% of cases are caused by *PROK2* and *PROKR2* mutations which exhibit an autosomal recessive form of transmission [10]. While isolated GnRH deficiency caused by a *CHD7* mutation is associated with CHARGE syndrome, there are also reports of it causing Kallmann syndrome in individuals without a CHARGE phenotype [11]. *FGF8* mutations, inherited in an autosomal dominant pattern, cause <5% of cases [10]. Mutations in some genes have been found to cause both anosmic and normosmic forms and include *FGFR1, PROK2, PROKR2, CHD7*, and *FGF8* [8].

Normosmic Types—The other 40% of cases of IHH are normosmic and inherited in an autosomal recessive pattern [10]. The most common reason for normosmic IHH is a mutation in the GnRH receptor (*GNRHR*), which accounts for 16–40% of cases [10]. Kisspeptin, a hypothalamic neuropeptide, and its receptor are encoded by the genes *KISS1*

and *KISS1R*, respectively. *KISS1* and *KISS1R* mutations in consanguineous families with normosmic IHH have been reported [12,13]. Patients with leptin (*LEP*) and leptin receptor (*LEPR*) mutations have severe obesity from a very young age and often develop HH, highlighting leptin's permissive role in the process of pubertal initiation and maturation [14]. *TAC3* and *TACR3* encode for neurokinin B, another hypothalamic neuropeptide, and its receptor and loss-of-function mutations in these genes are also found in families with normosmic IHH [15].

Despite the many mutations which are known to cause IHH, the etiology in the majority of cases remains enigmatic with 60–75% of anosmic and 50% of normosmic IHH cases being classified as idiopathic [10]. One of the most fascinating aspects of IHH is the potential for spontaneous recovery of the hypothalamic-pituitary-gonadal (HPG) axis later in life. Reversal of Kallmann syndrome and normosmic IHH has been seen in about 10% of cases, and therefore embarking on a trial-off of hormone replacement therapy in these patients is reasonable [16]. Comparable frequencies of reversible vs non-reversible IHH are reported with *FGFR1, PROKR2,* and *GNRHR* mutations [17]. In contrast, reversibility was more frequent with *TAC3* and *TACR3* mutations [17]. Spontaneous recovery with *ANOS1* mutations is rare [17].

Digenic Mutations—Two genes acting synergistically to produce a more severe phenotype of IHH than either single gene acting alone is known as a digenic mutation [18]. *FGFR1* and *NELF* mutations were found in one pedigree with Kallmann syndrome, and *GNRHR* and *FGFR1* mutations were found in a second pedigree with normosmic IHH [18]. The frequency of digenic mutations in IHH is estimated at 2.5% [19].

Mutations Affecting HPG Development—Mutations in the pituitary transcription factors PROP1, HESX1, and LHX3 affect the development of the pituitary gland and cause deficiencies of multiple pituitary hormones, including gonadotropins [14]. *PROP1* mutations lead to deficiencies of luteinizing hormone (LH), follicle-stimulating hormone (FSH), thyroid-stimulating hormone (TSH), growth hormone (GH), and prolactin [20]. Individuals with *PROP1* mutations are noted to initially have pituitary hyperplasia which later develops into hypoplasia [21]. The hormonal profile of *LHX3* mutations is similar to that seen in *PROP1* with deficiencies of LH, FSH, TSH, GH, and prolactin [22]. Mutations in *HESX1* are associated with septo-optic dysplasia (SOD) which is typified by the triad of pituitary hormone abnormalities, optic nerve hypoplasia, and midline brain defects such as agenesis of the corpus callosum or septum pellucidum [23]. When HH occurs in the setting of SOD, it is often present in combination with other pituitary hormone deficiencies [24].

Adrenal hypoplasia congenital is caused by a *DAX-1* mutation and is an X-linked recessive disorder [25]. *DAX-1* is an orphan nuclear receptor found in the adrenal gland, gonads, hypothalamus, and pituitary gonadotroph cells [26]. Due to its sex-linked inheritance pattern, all affected individuals are males [26]. Affected individuals tend to develop adrenal insufficiency as neonates or infants, although onset in later childhood can occur [25,26]. These boys fail to enter puberty due to HH [25,26].

Several mutations affect various levels of the HPG axis to cause HH. Mutations in the beta-subunit of LH and FSH are very rare [27]. Females with mutations in the beta-subunit of LH have normal pubertal development, but secondary amenorrhea and infertility [27]. Males have immature Leydig cells, testosterone deficiency, and impaired spermatogenesis [27]. A mutation in the beta-subunit of FSH results in pubertal delay and primary amenorrhea in females [28] while males have small testes, testosterone deficiency, and azoospermia [29].

Syndromes—Many syndromes include HH [6]. Three of the more well-known are Prader-Willi, Bardet-Biedl, and CHARGE syndromes, each of which will be highlighted here. Prader Willi syndrome most often occurs due to a de novo deletion of paternally inherited genes on chromosome 15q11-q13, but may also result from maternal uniparental disomy of chromosome 15 [30]. Several neuroendocrine abnormalities secondary to hypothalamic-pituitary dysfunction are present including GH insufficiency with associated short stature, hypogonadism, hypothyroidism, and obesity [30]. Genital hypoplasia is present at birth in both sexes, but is more noticeable in males as cryptorchidism is present in over 80% and may be seen with underdevelopment of the scrotum and small testes [30,31]. Puberty is often delayed or incomplete [31]. The hypogonadism in males was historically considered centrally mediated, but primary testicular failure, or a combination of both are now recognized [32]. Ovarian function in girls appears to be normal [33].

Features of Bardet-Biedl syndrome include retinal dystrophy, polydactyly, obesity, developmental delays, renal anomalies, genitourinary malformations in females, and HH in males [34]. The condition is inherited autosomal recessively, and 16 genes have been implicated, with the most common being *BBS1* and *BBS10* [34]. Mutations lead to cilia cell structure dysfunction which is thus thought to underlie the features of this condition [34].

CHARGE syndrome features include coloboma, heart malformations, choanal atresia, growth retardation, genital anomalies, and ear abnormalities. The majority of cases are de novo and caused by a *CHD7* gene mutation [35]. *CHD7* is expressed in the pituitary [36] and mutations in this gene mainly lead to HH, but GH deficiency and rarely hypopituitarism have also been described [35].

Hypergonadotropic Hypogonadism

In contrast to HH, in which the abnormalities reside within the hypothalamus or pituitary, the defect in hypergonadotropic hypogonadism is at the level of the gonads themselves. Hence, the condition which can be congenital or acquired, is referred to as primary hypogonadism and is characterized by elevated gonadotropin levels with low sex steroid hormone concentrations [5]. This review will cover congenital causes which occur secondary to chromosomal abnormalities, genetic mutations, or syndromes.

Sex Chromosomal Abnormalities—Turner syndrome (TS) is defined by the presence of one intact X chromosome with partial or complete absence of the second X chromosome in addition to characteristic clinical features [37]. The prevalence rate is 25 to 50 per 100,000 females [37]. Hypergonadotropic hypogonadism occurs secondary to primary ovarian failure which begins in utero with accelerated oocyte atresia and a severe reduction in follicle formation [38]. Spontaneous breast development occurs in about one-third of girls

[37], particularly in those with mosaicism compared to those with X-monosomy [39]. Spontaneous menarche may also occur in approximately 16.1% to 19% of girls, again more likely in those with mosaicism [39,40]. Nevertheless, the majority of girls with TS regardless of karyotype eventually require hormone replacement therapy due to lack of or arrested pubertal development [37,39].

Other X-chromosome abnormalities can also lead to primary ovarian failure. Translocations affecting either of the two critical regions Xq13→q22 and Xq22→q26 on the long-arm of the X-chromosome contribute to primary ovarian failure [41]. When the deletion is distal to Xq24, females often have either primary or secondary amenorrhea without short stature or other features of TS [37]. Primary hypogonadism is also a feature of other conditions of X-chromosome aneuploidy such as triple X syndrome [42].

The most common sex chromosome aneuploidy affecting males is Klinefelter syndrome with a prevalence of 1 in every ~660 males [43]. Klinefelter syndrome is characterized by an extra X-chromosome, and the most common karyotype is XXY. Classic clinical features are tall stature, gynecomastia, hypergonadotropic hypogonadism, infertility, small testes, and speech and learning difficulties. The condition often goes undiagnosed in the pediatric age range, with affected men typically presenting in their mid-30s [44] with infertility or hypogonadism [43]. While the onset of puberty is unremarkable, it does not progress normally and testicular volume typically stalls out at ~6 mL [44]. Subsequently, the testicles shrink due to hyalinization of the seminiferous tubules and loss of germ cells [43]. Leydig cell hyperplasia is also seen histologically and is likely due to elevated LH concentrations [43].

Syndromes—Fragile X Syndrome results from expansion of CGG repeats in an untranslated region of the *FMR1* gene. Greater than 200 repeats result in silencing of the gene, but a repeat length of 55 to 200 is classified as a premutation carrier. Varying degrees of ovarian dysfunction occur in female premutation carriers [45], and range from regular menses with infertility due to primary ovarian insufficiency, to oligomenorrhea or amenorrhea prior to age 40 due to premature ovarian failure [46].

Galactosemia most often occurs secondary to impaired activity of the enzyme galactose-1-phosphate uridyltransferase due to a mutation in the *GALT* gene, resulting in the inability to break down galactose. This metabolic disorder results in severe vomiting, diarrhea, failure to thrive, cataracts, hepatomegaly with jaundice, and potentially *E. Coli* sepsis after the introduction of milk shortly after birth [47]. Despite lifelong adherence to dietary restriction of galactose, 80% of females with the condition develop primary ovarian failure [48]. Primary gonadal failure is absent in males [48]. While the etiology is not completely understood, studies suggest that the ovarian failure occurs very early in the prenatal or perinatal period due to direct toxicity of galactose or its metabolites on ovarian tissue [47,49].

FSH and LH Receptor Dysfunction—Mutations in the FSH and LH receptor are uncommon causes of hypergonadotropic hypogonadism in the general population. In 75 females with hypergonadotropic hypogonadism from 13 Finnish families, 22 females had an

inactivating point mutation in the FSH receptor gene [50,51]. Females with homozygous mutations were infertile demonstrating the importance of FSH for follicular maturation [50,51]. However, some of their brothers also had homozygous mutations, but did not have complete infertility [51]. Instead they had varying degrees of oligospermia suggesting that FSH is important but not essential for spermatogenesis [51].

Depending on the severity of the LH receptor mutation, the genital phenotype in 46XY individuals ranges from mild ambiguity to complete female-appearing external genitalia [52]. 46XX individuals with LH receptor mutations have a milder presentation with normal secondary sexual characteristics, but with anovulatory amenorrhea and low estrogen levels [53].

Genetic etiologies of both hypogonadotropic and hypergonadotropic hypogonadism are found in Table 2.

Precocious Puberty

Precocious puberty refers to secondary sexual development ensuing prior to the norms for racial or ethnic background and traditionally has been defined as prior to age 8 in girls and age 9 in boys [54,55]. Central precocious puberty (CPP) involves early activation of the HPG axis and laboratory evidence of elevated random or stimulated gonadotropin and sex steroid levels. Peripheral precocious puberty (PPP) describes pubertal onset that does not originate from the HPG axis and levels of gonadotropins are suppressed in the setting of elevated sex steroid levels. Causes of both central and peripheral precocious puberty include genetic, acquired, and idiopathic conditions [56,57]. This review will be limited to CPP and PPP arising from genetic mutations and observed in the context of some specific syndromes.

Central Precocious Puberty—The four known monogenic causes of CPP arise from mutations in kisspeptin (*KISS1*), the kisspeptin receptor (*KISS1R*), makorin RING-finger protein 3 (*MKRN3*), and delta-like homolog 1 (*DLK1*) [56]. Historically the majority of cases of CPP are idiopathic, but since 27.5% of cases have a positive family history, a genetic cause is suspected [58]. Kisspeptin, a stimulator of GnRH neurons, is considered the primary “gatekeeper” of puberty [59]. Activating mutations in the *KISS1* and *KISS1R* genes have been found thus far in one patient with CPP each [58–61] and appear to be an uncommon cause of CPP [62,63]. Both mutations cause delayed degradation of the mutant protein resulting in prolonged intracellular signaling and subsequent amplification of their physiologic effect [64].

MKRN3 acts as an inhibitor of pubertal initiation and therefore loss-of-function mutations result in CPP [64]. In a sample of 38 healthy girls, MKRN3 levels declined prior to the onset of puberty and were lower in subjects with early puberty compared to age-matched prepubertal controls [65]. Mutations in *MKRN3* are the most common cause of familial cases of CPP [64] and were originally described in 5 of 15 affected families [66]. *MKRN3* is a maternally imprinted and paternally expressed gene, and accordingly all subjects exhibiting the phenotype inherit the mutation from their fathers [66]. Sporadic MKRN3 mutations have also been described [67].

DLK1, also known as preadipocyte factor-1, is widely expressed in several tissues prenatally, but after birth is mainly expressed in the adrenals, pituitary, and ovaries [64]. Although DLK1 is known to be a potent inhibitor of adipocyte differentiation, its relation to pubertal onset is not well understood [68]. However, it was found to be expressed in several mouse hypothalamic nuclei [68]. A loss-of-function *DLK1* mutation was found in five female family members and their serum DLK1 levels were undetectable [69]. Similar to *MKRN3, DLK1* is a maternally imprinted and paternally inherited gene, so only females who inherited the mutation from their father had CPP [69]. In a larger sample of 60 girls with idiopathic CPP representing 23 familial cases, no mutations in *DLK1* were found, and therefore *DLK1* mutations are likely a rare cause of CPP [70]. Interestingly, adult women with a *DLK1* mutation and history of CPP exhibit a distinct metabolic phenotype marked by higher rates of obesity, dyslipidemia, and PCOS compared to controls [71]. Thus, DLK1 may represent an important link between metabolism and reproduction.

CPP has been reported as part of several genetic syndromes including Temple syndrome (90% of cases), Russell-Silver Syndrome (up to 25% of cases), Williams syndrome (10–18% of cases), and Prader-Willi syndrome (4–10% of cases) [64]. Children with neurofibromatosis type 1, particular in the setting of optic pathway gliomas, are also at increased risk for CPP [72].

Peripheral Precocious Puberty—McCune-Albright Syndrome (MAS) is characterized by the triad of café-au-lait macules, fibrous dysplasia, and precocious puberty. Other endocrinopathies such as Cushing syndrome, growth hormone excess, and hyperthyroidism can also occur. It is caused by a post-zygotic mutation in the guanine nucleotide binding protein alpha stimulating gene (*GNAS1*), which leads to constitutive activation of the adenylyl cyclase system with subsequent cell proliferation and hormone production [73]. Since it is a post-zygotic mutation, it is not inherited from an individual's parents, and therefore cannot be passed down to offspring. It is an extremely heterogenous disorder due to mosaicism. Therefore, depending on which cells are affected, the severity and clinical findings vary greatly [57]. PPP is most commonly diagnosed in girls aged 1–5 years, and results from autonomous production of estrogen from large unilateral ovarian cysts [74]. MAS in girls presents with sudden onset of painless vaginal bleeding and minimal breast development [74]. The breast development and other signs of MAS may be missed leading to unnecessary oophorectomy in girls mistakenly thought to have an ovarian granulosa cell tumor [57,74,75]. PPP in boys with MAS is much less common, but presents with early secondary sexual development and accelerated linear growth velocity. A Sertoli-cell only *GNAS1* mutation has also been described in boys with MAS resulting in testicular enlargement without PPP [76].

Familial male-limited precocious puberty (FMPP) has an autosomal dominant inheritance pattern and is often associated with a positive family history, but may also arise de novo [57]. The condition is caused by an activating mutation of the LH receptor which results in autonomous production of testosterone by testicular Leydig cells. While females are asymptomatic carriers due to the requirement for both LH and FSH for ovarian estrogen production, males present with virilization prior to age 4 [77]. As in other forms of PPP in

boys, classic findings include virilization such as an enlarged phallus and pubic hair that is out of proportion to a smaller than expected testicular volume [57,75].

Genetic etiologies of both CPP and PPP are summarized in Table 3.

Treatment of Delayed and Precocious Puberty

The primary goal of treatment in hypogonadism is to mimic normal pubertal progression utilizing replacement of sex steroids [5]. There are a multitude of different options for sex steroid replacement and no universally accepted standard treatment algorithm exists. Representative formulations and suggested doses for estrogen and progesterone replacement in girls [5,37,78–80] and testosterone replacement in boys [5,43,78,81] are summarized in Tables 4 and 5, respectively. The primary goals for the management of CPP and PPP are preservation of height potential and prevention of further pubertal progression [55,57]. GnRH analogs (GnRHas) have a long history of safety and efficacy and are standard of care for the treatment of CPP [56]. The number of extended release GnRHa preparations has steadily increased and includes 3-monthly and 6-monthly injectables and a subcutaneous implant that is marketed for annual use, but provides HPG axis suppression for at least 2 years [82,83]. Not all long-acting GnRHas result in equivalent suppression of the HPG axis, however. The 11.25 mg 3-monthly GnRHa formulation is associated with less suppression than the 30 mg dosage [54], and none of the injectable preparations are as potent as the histrelin implant [84]. While these observations make prescribing decisions more challenging, little comparative information is available and it is unknown whether disparities in the degree of biochemical suppression will translate into meaningful differences in clinical outcomes such as height [85]. Ongoing controversies in the treatment of CPP include whether a brain MRI is necessary in all cases [86], when therapy should be discontinued, and which girls should be treated [87]. Medications for treating PPP in boys with FMPP have been largely successful [75]. In girls with MAS, treatment of PPP remains challenging and approaches often have limited success [75]. Formulations and doses of GnRH analogs [55,88] and therapeutic options for MAS and FMPP [57,75] are shown in Tables 6 and 7, respectively.

Summary

The genetic disorders contributing to either delayed or precocious puberty demonstrate the highly complex role of genetics in the regulation of puberty. There are numerous genetic etiologies of delayed or precocious puberty ranging from single gene mutations, digenic mutations, congenital syndromes, and chromosomal abnormalities to cases which remain idiopathic. Future research expanding our current understanding and the discovery of new mutations underlying idiopathic cases are critical for improving our diagnostic, prognostic, and therapeutic outcomes for children and adults with these conditions.

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Synopsis

Delayed puberty may signify a common variation of normal development, or indicate the presence of a pathologic process. Constitutional delay of growth and puberty is a strongly familial type of developmental pattern and accounts for the vast majority of children who are “late bloomers”. Numerous genetic abnormalities leading to permanent hypogonadism presenting as delayed puberty have also been identified. Several mutations are known to cause isolated hypogonadotropic hypogonadism with or without anosmia. Other genetic causes of hypogonadotropic hypogonadism arise from defects at various levels of the hypothalamic-pituitary-gonadal (HPG) axis or involve genetic syndromes. Individuals with sex chromosomal abnormalities frequently have hypergonadotropic hypogonadism. There are currently four known monogenic causes of central precocious puberty (CPP). Genetic causes of peripheral precocious puberty include McCune-Albright syndrome (MAS) and Familial male-limited precocious puberty (FMPP). The primary treatment goal in children with hypogonadism is to mimic normal pubertal progression, while the primary aims for the management of precocious puberty are preservation of height potential and prevention of further pubertal development.

Key Points

- Delayed puberty can be a common variant or be due to a defect in the HPG axis.
- Isolated cases of hypogonadotropic hypogonadism with and without anosmia are caused by several mutations, but the majority of cases remain idiopathic.
- Sex chromosomal aneuploidies such as Turner syndrome and Klinefelter syndrome are important causes of hypergonadotropic hypogonadism.
- Four monogenic mutations (*KISS1, KISS1R, MKRN3, DLK1*) are known to cause CPP.
- Genetic causes of peripheral precocious puberty include MAS and FMPP.
- Treatment of delayed puberty focuses on replacement of sex steroids. The mainstay of treatment for CPP is gonadotropin-releasing hormone analogs. While effective therapies exist for FMPP, treatment approaches in MAS have variable and limited success rates.

Table 1.

Acronyms and Full Titles of Gene Mutations Associated with Delayed and Precocious Puberty

Acronym	Full-Length Title
ANOS1	Anosmin 1
FGFR1	Fibroblast Growth Factor Receptor 1
PROK2	Prokineticin 2
PROKR2	Prokineticin Receptor 2
CHD7	Chromodomain Helicase DNA-Binding Protein 7
FGF8	Fibroblast Growth Factor 8
GNRHR	Gonadotropin-Releasing Hormone Receptor
KISS1	Kisspeptin 1 Metastasis Suppressor
KISS1R	Kisspeptin 1 Receptor
LEP	Leptin
LEPR	Leptin Receptor
TAC3	Tachykinin 3
TACR3	Tachykinin Receptor 3
NELF	Nasal Embryonic Luteinizing Hormone-Releasing Hormone Factor
IL17RD	Interleukin 17 Receptor D
PROP1	PROP Paired-Like Homeobox 1
HESX1	Homeobox Gene Expressed in Embryonic Stem Cells
LHX3	LIM Homeobox Gene 3
DAX1	Dosage-Sensitive Sex Reversal-Adrenal Hypoplasia Congenita Critical Region on the X Chromosome, Gene 1
BBS	Bardet-Biedl Syndrome
FMR1	Fragile X Mental Retardation 1
GALT	Galactose-1-Phosphate Uridylyltransferase
MKRN3	Makorin Ring Finger Protein 3
DLK1	Delta Like Non-canonical Notch Ligand 1
GNAS1	Guanine Nucleotide-Binding Protein, Alpha-Stimulating Activity Polypeptide 1

Table 2.

Genetic Etiologies of Hypogonadotropic and Hypergonadotropic Hypogonadism

Abnormality	Mutation or Abnormality	Important Clinical Highlights
Hypogonadotropic hypogonadism		
• Isolated		
○ Anosmic	*ANOS1, FGFR1, PROK2, PROKR2, CHD7, FGF8*	*ANOS1:* unilateral renal agenesis, bimanual synkinesis *FGFR1:* cleft palate, dental agenesis, skeletal anomalies
○ Normosmic	*GNRHR, KISS1, KISS1R, LEP, LEPR, TAC3, TACR3*	Most common is *GNRHR. LEP* and *LEPR* with early-onset obesity.
○ Anosmic or Normosmic	*FGFR1, PROK2, PROKR2, CHD7, FGF8*	*CHD7* may be seen without CHARGE phenotype
• HPG axis		
○ Pituitary transcription factors	*PROP1, HESX1, LHX3*	*PROP1* & LHX3: LH, FSH, TSH, GH, and prolactin deficiencies HESX1: Associated with SOD
○ Adrenal hypoplasia congenital	*DAX-1*	Adrenal insufficiency at an early age
○ Gonadotropins	LH and FSH beta-subunit	LH beta-subunit: 2° amenorrhea in females. Impaired spermatogenesis in males. FSH beta-subunit: 1° amenorrhea in females. Azoospermia in males.
• Syndromes		
○ Prader-Willi	Paternal deletion or maternal uniparental disomy of chromosome 15q11-q13	Genital hypoplasia both sexes. Cryptorchidism in 80% of males.
○ Bardet-Biedl	*BBS* genes (most common *BBS1* & *BBS10)*	Genitourinary malformations in females. Hypogonadism in males.
○ CHARGE	*CHD7*	Expressed in pituitary, mainly hypogonadism, may have GH deficiency
Hypergonadotropic hypogonadism		
• Sex Chromosome Abnormality		
○ Turner syndrome	Partial or complete absence of 2^{nd} X- chromosome	Spontaneous breast development and menarche more common in mosaic genotype
○ Klinefelter syndrome	Extra X-chromosome (most common XXY)	Testicular volume maxes ~6 mL, then shrinks down. Often men present in mid-30s with infertility.
• Syndromes		
○ Fragile X premutation carrier	55–200 CGG repeats in *FMR1*	Premutation carriers only with infertility, oligo or amenorrhea
○ Galactosemia	*GALT*	80% of females with primary ovarian failure
• Gonadotropin receptors LH and FSH receptor	LH and FSH receptor	LH receptor: Anovulatory amenorrhea in females. Genital ambiguity in 46XY individuals. FSH receptor: Infertility in females. Impaired spermatogenesis in males.

Table 3.

Genetic Etiologies of Central and Peripheral Precocious Puberty

Abnormality	Mutation or Abnormality	Important Clinical Highlights
Central precocious puberty		
• Monogenic causes	*KISS1, KISS1R, MKRN3, DLK1*	*MKRN3* most common cause of familial CPP. *KISS1, KISS1R,* and *DLK1* are very uncommon. *DLK1* associated with metabolic syndrome phenotype.
• Syndromes		
○ Temple	Maternal uniparental disomy or paternal deletion of chromosome 14q32.2	CPP in 90% of cases Loss of DLK1 expression
○ Russell-Silver	Hypomethylation of chromosome 11p15 or maternal uniparental disomy of chromosome 7	CPP in up to 25% of cases
○ Williams	Deletion of chromosome 7q11.23	CPP in 10–18% of cases
○ Prader-Willi	Paternal deletion or maternal uniparental disomy of chromosome 15q11-q13	CPP in 4–10% of cases
○ Neurofibromatosis type 1	*NF1*	Increased risk particularly in setting of optic pathway glioma
Peripheral precocious puberty		
• Syndromes		
○ McCune-Albright	Post-zygotic mutation in *GNAS1*	PPP most commonly presents in girls aged 1–5 years as sudden onset of painless vaginal bleeding
○ Familial male-limited	Activating mutation of LH precocious puberty receptor	Virilization in males prior to age 4. Enlarged phallus and pubic hair out of proportion to the small testicular volume.

Table 4.

Commonly Used Estrogen and Progesterone Formulations for Hypogonadism in the United States

Estrogen Formulation	Brand Name	Initiation Dose[1]	Adult Dose
Transdermal			
• Patch	Vivelle	6.25–12.5 mcg twice weekly	25–100 mcg twice weekly
Oral			
• Micronized 17β-estradiol	Estrace	0.25 mg daily	1–4 mg daily
Progesterone Formulation		**Notes for Clinical Care**	**Adult Dose**[2]
Oral			
• Medroxyprogesterone acetate • Micronized progesterone	Provera Prometrium	Progestin added after first episode of vaginal bleeding or after 2 years of estrogen treatment	10 mg daily for 10 days each month 100–200 mg daily for 10–21 days each month or continuously
Estrogen and Progesterone Formulation		**Notes for Clinical Care**	**Adult Dose**
Oral Contraceptive Pill (OCP)		Do not use OCP to initiate puberty.	Multiple types with various doses of estrogen and progestin.

[1] Increase estradiol dose every 6 months over 2–3 year period with goal of adult dosing range.

[2] Given with estradiol.

Table 5.

Commonly Used Testosterone Formulations for Hypogonadism in the United States

Testosterone Formulation	Brand Name	Initiation Dose[1]	Adult Dose
Transdermal			
• Testosterone patch	Androderm	Do not use transdermal route to initiate puberty.	2–6 mg daily
• Testosterone gel	Androgel (1.62%)		20.25–81 mg daily
Intramuscular[2]			
• Testosterone cypionate	Depot-Testosterone	50–100 mg monthly	200–250 mg every 2–4 weeks
• Testosterone enanthate	Delatestryl	50–100 mg monthly	200–250 mg every 2–4 weeks
Subcutatneous			
• Testosterone enanthate	Xyosted	Do not use Xyosted to initiate puberty.	50–100 mg once weekly

[1] Increase testosterone dose every 3–6 months over 3–4 period with goal of adult dosing range. Follow trough serum testosterone levels and adjust adult dose accordingly to maintain testosterone in midnormal range.

[2] Can be given via subcutaneous route with doses of 50–150 mg weekly.

Table 6.

Gonadotropin-Releasing Hormone Analogs used in Central Precocious Puberty in the United States

Formulation	Frequency	Dose	Route
Leuprolide	Monthly 3-monthly	0.2–0.3 mg/kg every 1 month 11.25 or 30 mg every 3 months	Intramuscular injection Intramuscular injection
	6-monthly	45 mg every 6 months (89)	Subcutaneous injection
Triptorelin	6-monthly	22.5 mg every 6 months	Intramuscular injection
Histrelin	1–2 years	50 mg every 1–2 years	Subcutaneous implant

Table 7.

Therapeutic Options for Use in McCune-Albright Syndrome & Familial Male-Limited Precocious Puberty

McCune-Albright Syndrome	Mechanism of Action
Females	
• Letrozole	Third-generation aromatase inhibitor
• Tamoxifen	Selective estrogen receptor modulator
• Fulvestrant	Estrogen receptor antagonist
Males	
• Letrozole	Third-generation aromatase inhibitor
• Anastrozole	Third-generation aromatase inhibitor
• Bicalutamide[1]	Non-steroidal androgen receptor antagonist
Familial Male-Limited Precocious Puberty	**Mechanism of Action**
Aromatase Inhibitor	
• Letrozole	Third-generation aromatase inhibitor
• Anastrozole	Third-generation aromatase inhibitor
Antiandrogen[1]	
• Bicalutamide	Non-steroidal androgen receptor antagonist
• Spironolactone	Weak anti-androgenic agent

[1]Used in combination with an aromatase inhibitor.