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Genetics of Pubertal Timing

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Abstract

Purpose of review—To summarize advances in the genetics underlying variation in normal pubertal timing, precocious puberty, and delayed puberty, and to discuss mechanisms by which genes may regulate pubertal timing.

Recent findings—Genome-wide association studies have identified hundreds of loci that affect pubertal timing in the general population in both sexes and across ethnic groups. Single genes have been implicated in both precocious and delayed puberty. Potential mechanisms for how these genetic loci influence pubertal timing may include effects on the development and function of the GnRH neuronal network and the responsiveness of end-organs.

Summary—There has been significant progress in identifying genetic loci that affect normal pubertal timing, and the first single-gene causes of precocious and delayed puberty are being described. How these genes influence pubertal timing remains to be determined.

Keywords

pubertal timing; central precocious puberty; delayed puberty; genetics; genome-wide association

INTRODUCTION

Puberty is a period of remarkable physical and psychological development that results in sexual maturation. Precocious and delayed puberty can be sources of distress, and there is compelling evidence that variation in pubertal timing may affect risks for conditions such as cardiovascular disease, breast cancer, and depression [1, 2**, 3]. Despite the strong heritability of pubertal timing, our understanding of the underlying genetics is limited. Recent advances have started to reveal the genetic background of normal pubertal timing and the first single-gene causes of precocious and delayed puberty. In this review, we discuss recent developments in the genetics of normal pubertal timing, central precocious puberty,

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Conflicts of Interest

Y.-M.C. delivered a presentation on the genetics of pubertal timing at an unrestricted educational symposium sponsored by Endo Pharmaceuticals held at the International Meeting of Pediatric Endocrinology in September 2017.

and delayed puberty and discuss potential mechanisms for how implicated genes may affect pubertal timing.

VARIATION IN NORMAL PUBERTAL TIMING

The timing of normal pubertal onset varies substantially and is influenced by both genetic and environmental factors, with genetic factors accounting for an estimated 50–75% of the variation [4–6]. While numerous studies have examined associations between candidate genes and pubertal timing in small to moderate-sized cohorts [7–22], this section will focus on large-scale genome-wide association studies (GWAS), which provide the most definitive results to date, and on a series of studies on variants in *FSHR*, the gene encoding the FSH receptor.

Genome-Wide Association Studies

In the last decade, GWAS have been used to identify genetic loci that affect normal pubertal timing (Table 1). In 2009, four independent GWAS reported the first evidence that common genetic variants can influence pubertal timing [23–26]. Subsequent studies have used ever-larger cohorts, and a GWAS in 2017 used data in 368,888 women to identify 389 loci that influence pubertal timing [2**, 33]. These loci affect multiple biological pathways and sites of action, which are further discussed below.

Most GWAS have used recalled age at menarche as a retrospective marker of pubertal timing in females. In males, age at voice breaking has been used as a similar marker. GWAS in men have largely revealed significant overlap between the sexes in the genetic factors that influence pubertal timing. However, some loci show different effect sizes or even effects in opposite directions [35, 37]. Potential mechanisms for these sex-specific effects on pubertal timing have been recently discussed by Cousminer et al. [37].

The most recent 2017 GWAS examined not only pubertal timing within the normal range but also early and late pubertal timing. This analysis suggested that, in girls, common genetic variants contribute more to early than late pubertal timing, and that in boys the opposite is true [2**]. The mechanisms underlying this sex difference are not clear [37], but this difference may explain why precocious puberty is more likely to be idiopathic in girls than in boys and may also explain, at least partially, why precocious puberty appears to be more common in girls and delayed puberty in boys [2**, 38, 39].

The above GWAS were conducted in cohorts of European ancestry. GWAS on age at menarche have also been conducted in non-European populations to determine the effect sizes of previously identified GWAS loci in different ethnic backgrounds as well as to potentially identify new loci. These GWAS, conducted in women of Hispanic [28], African American [29, 30], Japanese [31], Korean [34, 36], and Chinese [36*] origin, did not identify any additional genome-wide significant loci (Table 1), but statistical power was limited by the relatively smaller sample sizes in these studies (approximately 3,500 to 18,000) [28–31, 34, 36*]. These genome-wide studies, as well as additional studies examining select loci in Filipino [40], Chinese [41], American Indian [42], and Native Hawaiian [42] cohorts, have demonstrated possible differences in effect sizes between ethnic

groups. Thus, it appears that there is considerable overlap across populations in genetic loci that influence pubertal timing, though the specific effects of each locus may vary.

Studies in *FSHR*

A series of studies have analyzed variants near *FSHR*, the gene encoding the FSH receptor, that appear to decrease signaling through the receptor. These variants have been associated with later age at testicular growth in boys and thelarche in girls [43, 44*, 45**]. However, recent GWAS have not associated these *FSHR* variants with age of menarche in girls or age at voice breaking in boys [2**]. A recent study investigating effects of several candidate gene variants on various hallmarks of puberty, found that a variant in *LIN28B*, the gene most strongly associated with variation in pubertal timing across multiple GWAS, affected timing of both thelarche and menarche, but variants in *FSHR* affected timing of thelarche but not menarche [45**]. At puberty, FSH stimulates ovarian production of estradiol, which stimulates growth of breast tissue, resulting in thelarche, one of the earliest hallmarks of female puberty. In contrast, menarche is a late event and likely involves maturation at multiple levels of the hypothalamic-pituitary-gonadal axis. Thus, it is possible that genes like *LIN28B*, which has been proposed to act in the hypothalamus, may impact all pubertal milestones, but genes like *FSHR*, which act peripherally, may preferentially affect thelarche with a smaller effect on menarche [45**].

Other Sources of Genetic Variation

Currently, the 389 loci identified through GWAS account for 7.4% of the variation in normal pubertal timing [2**]; GWAS for many other traits and conditions have similarly explained only a small proportion of variation [46]. It is possible that there are many more variants yet to be discovered in GWAS with even larger cohorts.

In addition, factors beyond single-nucleotide polymorphisms may contribute to variation in pubertal timing, factors including copy number variation or epigenetic changes [47, 48]. A duplication near the *DBI* (diazepam binding inhibitor) gene, believed to decrease testosterone and estrogen levels through effects on GABA signaling in mice, has been linked to age at menarche [47]. The latest GWAS associated lysine-specific demethylase genes with age at menarche, raising the possibility that epigenetic changes, including methylation, may also influence pubertal timing [2**]. Findings that global DNA methylation in adult women and epigenetic age (as determined by methylation of specific loci) in adolescent girls may be associated with age at menarche provide further support for this concept [49, 50].

CENTRAL PRECOCIOUS PUBERTY

MKRN3

In 2013, mutations in *MKRN3* emerged as an important genetic cause of central precocious puberty (CPP) in both boys and girls from whole-exome sequencing in multiple unrelated families. Loss-of-function mutations in *MKRN3* both familial and sporadic cases of CPP have since been identified in various ethnic groups in the U.S., Brazil, Israel, Korea, Taiwan, and eight European nations [51–53, 54*, 55, 56]. Case series of families with multiple affected members have estimated the prevalence of *MKRN3* mutations to be 33 to 46% in

familial cases [57–59] and 0.4 to 3.8% in sporadic cases [52, 53, 60], and two small case series, including one in boys, have suggested even higher rates [53, 61*].

MKRN3 is a maternally imprinted gene; that is, only the paternal allele is expressed. Consistent with this imprinting pattern, only individuals who inherit an *MKRN3* mutation from their father develop CPP [51]. In large familial cases, there is complete penetrance of *MKRN3* mutations. However, two recent case reports suggested that both male and females with paternally inherited *MKRN3* defects can sometimes be asymptomatic carriers [54*, 62].

Patients with CPP due to loss-of-function mutations in *MKRN3* appear to be similar to CPP patients without *MKRN3* mutations, with a median age of pubertal onset of 6.0 years in girls (range of 3.0 to 7.8 years) and 8.3 years in boys (range of 5.9 to 9.0 years) [51–54*, 56, 59, 61*]. *MKRN3* mutations do not appear to cause any phenotypes other than CPP. The exact mechanism by which defects in *MKRN3* lead to early activation of the hypothalamic-pituitary axis is unknown. *MKRN3* encodes a protein that resembles E3 ubiquitin ligases, which facilitate ubiquitination of target proteins, leading to degradation by the proteasome or, in some cases, modification of protein function [63*]. Studies in mice show that *Mkn3* is expressed in the hypothalamus, and its expression decreases with sexual maturation [63*]. *MKRN3* has therefore been postulated to have an inhibitory influence on reproductive endocrine activity in the hypothalamus in prepubertal children [64, 65].

DLK1

A defect in another imprinted gene, *DLK1*, was identified in 2017 through linkage analysis and whole-genome sequencing in a large family with multiple members with CPP [66**]. A ~14 kb deletion in *DLK1* was found to segregate with all four affected female members from a Brazilian family of African descent. Previously, deletions in *DLK1* and surrounding genes had been identified as the cause of Temple Syndrome, a rare genetic disorder associated with CPP [67]. Subsequent screening for *DLK1* mutations in an additional 19 individuals with CPP in the same study and in 60 girls with CPP in a separate study did not identify any rare variants or deletions, suggesting *DLK1* mutations are a relatively rare cause of central precocious puberty [53, 66**].

The role of *DLK1* in the regulation of pubertal timing is unknown. Studies in mice show that *Dlk1* is expressed in the hypothalamus, and *in vitro* studies demonstrate that *DLK1* may be a regulator of Notch signaling, which appears to be an important component of kisspeptin neuronal development in mice [66**, 68, 69]. Kisspeptin stimulates secretion of GnRH in the hypothalamus; thus, *DLK1* may affect GnRH secretion through the regulation of kisspeptin [66**].

The GWAS discussed above identified variants near the *MKRN3* and *DLK1* loci and specifically associated paternally-inherited variants with pubertal timing [2**, 33, 65]. These findings provide further evidence for the critical role of *MKRN3* and *DLK1* in the regulation of pubertal timing and demonstrate genetic links between the rare disease of central precocious puberty and normal variation in pubertal timing in the general population.

Kisspeptin and KISS1R

Gain-of-function mutations in the genes encoding kisspeptin and its receptor, *KISS1* and *KISS1R*, respectively, have also been suggested to be causes of CPP [70*]. In 2008, a rare heterozygous mutation in *KISS1R* was identified in a Brazilian girl with CPP; this mutation led to prolonged intracellular signaling following kisspeptin binding [71]. A subsequent study in 2010 identified a rare heterozygous variant in *KISS1* thought to confer resistance to degradation in a boy with CPP [72]. Studies have also investigated the role of common variants in *KISS1* and *KISS1R* in individuals with CPP; these studies have suggested potential associations, but because of the small size of these studies, further replication studies are needed to confirm these findings [70*, 73]. Thus, variants in the kisspeptin pathway may be associated with central precocious puberty in some cases.

Other Candidate Genes

Investigations of both common and rare variants in genes identified in GWAS (*LIN28B*, *TACR3*, *LEPR*, and *ESR1* [2**, 33]) have not revealed any definitive associations with precocious puberty [70*, 74–79]. Though some small-scale candidate SNP or gene-association studies of additional candidate gene *GNRH1*, *LHB*, *FSHB*, *TTF1*, *EAP1*, *NPVF*, *NPFFR1* (genes biologically linked to gonadotropin signaling) [80–82] and *CYP19A1*, *CYP11A1*, *CYP17*, and *CYP11B1* (genes encoding steroidogenesis enzymes) [83, 84] have reported potential associations, the small size of these studies preclude any definitive conclusions.

SELF-LIMITED DELAYED PUBERTY

In self-limited delayed puberty (also called constitutional delay), pubertal onset is delayed but occurs spontaneously prior to age 18 years [85]. In contrast, in idiopathic hypogonadotropic hypogonadism (IHH), another condition that presents with delayed puberty, puberty does not start or is incomplete by adulthood [86]. In some cases, individuals with IHH undergo “reversal,” that is, activation of the HPG axis after age 18 years [87]. This section will focus on the recent developments in the genetics of self-limited delayed puberty and investigations into potential genetic links between these disorders.

IGSF10

IGSF10 was the first gene to be associated with self-limited delayed puberty through a whole-exome sequencing study of 76 affected individuals from 18 unrelated families [88]. Four heterozygous, potentially pathogenic missense variants in *IGSF10* were identified in 28 individuals with delayed puberty from 10 families, and in 7 of these families these variants segregated fully with delayed puberty. Functional *in vitro* studies showed failed excretion and cytoplasmic retention of the mutant proteins [88]. Of note, a recent study did not identify significantly enrichment of *IGSF10* mutations in individuals with delayed puberty compared to controls, but the high rate of variation in *IGSF10* (a large gene) in control populations makes such enrichment difficult to demonstrate [89*].

The precise role of *IGSF10* in human pubertal timing is yet to be elucidated. Studies in mouse and zebrafish models suggest that *IGSF10* is required for the proper migration of

GnRH neurons [88]. How defects in the GnRH neuronal network could result in delayed puberty is discussed further below.

Links to Idiopathic Hypogonadotropic Hypogonadism

Several studies in the last decade have investigated the hypothesis that self-limited delayed puberty and IHH share a genetic basis. Though initial studies examining individual IHH genes did not conclusively demonstrate such a genetic link [7, 90–92], a recent study using whole-exome sequencing to screen a panel of 21 IHH genes identified enrichment of potentially pathogenic variants in IHH genes in patients with delayed puberty compared to controls [93]. Of note, variants in the genes *TAC3* and *TACR3*, which encode neurokinin B and its receptor, were identified in multiple individuals with delayed puberty. The neurokinin B pathway has also been implicated in IHH with reversal, as well as in the variation of normal pubertal timing in GWAS; thus, neurokinin B signaling appears to have a critical influence on pubertal timing [2**, 87].

However, another study in Finnish individuals with delayed puberty did not identify an enrichment of mutations in a panel of 24 IHH genes in individuals with delayed puberty compared to controls [89*]. The apparent discrepancy between these studies could be due to differences in how mutations were defined [89*, 93].

Other Candidate Gene Analyses

Candidate genes from disorders that include delayed puberty or IHH as a feature have been proposed, including *LEP* and *LEPR* [94, 95], *IGSF1* [96], *IGFALS* [97], and *GHSR* [98]. Studies investigating the role of common variants in *LEP*, *LEPR*, and *IGALS* have not demonstrated an association with delayed puberty [94, 97]. Although rare-variant studies have identified two variants in *GHSR* (which encodes the ghrelin receptor) and one in *LEP* (which encodes leptin), whether rare variants in these genes are more common in individuals with delayed puberty compared to the general population is unclear [95–98]. An additional investigation in *LIN28B*, a gene identified in prior GWAS, did not identify any variants in 145 individuals with delayed puberty [2**, 99].

POTENTIAL MECHANISMS FOR REGULATING PUBERTAL TIMING

It has been proposed that puberty starts in the brain [100], yet the genes identified in the above studies have potential roles throughout the hypothalamic-pituitary-gonadal axis (Figure 1). How could these genes affect pubertal timing?

The earliest known physiologic event in puberty is an increase in pulsatile GnRH secretion from the hypothalamus; the mechanisms that determine the timing of this event is determined are largely unknown [101]. The first physical signs of puberty, such as testicular growth in boys and thelarche in girls, occur months to years after this initial increase in GnRH secretion [102], and voice breaking in boys and menarche in girls occur even later [2**].

Given this physiology, there are at least three potential mechanisms for variation in the timing of appearance of physical hallmarks of puberty (Figure 2). First, there may be

differences in the timing of the initial emergence of reproductive endocrine activity (Figure 2B). The genes *KISS1*, *KISS1R*, *TAC3* and *TACR3* encode signaling molecules and receptors that promote GnRH secretion and may function as part of this putative pubertal “switch” [2**, 86].

Second, differences in GnRH neuronal activity or in downstream signaling events could alter the rate at which reproductive hormones rise after this initial activation (Figure 2C). This mechanism could explain how genes involved in the development and migration of GnRH neurons, such as the *ANOS1* gene (also known as *KAL1*) affect pubertal timing [2**, 86].

Third, end-organ responsiveness to reproductive hormones may vary, thus changing the “threshold” for the degree of reproductive endocrine activity needed to induce physical characteristics of puberty (Figure 2D). This mechanism could explain how variants near the FSH receptor gene, *FSHR*, affect the timing of testicular growth in boys and breast development in girls [43, 44*, 45**].

These various mechanisms, which are not mutually exclusive, emphasize that puberty is not a single event but rather a process that unfolds over time, and that there has already been significant reproductive endocrine activity by the time physical hallmarks of puberty become apparent. Future studies may reveal additional mechanisms for variation in pubertal onset.

CONCLUSION

The last decade has seen significant progress in the identification of genes that affect pubertal timing, with the discovery of hundreds of common genetic variants that affect normal pubertal timing and the first single-gene causes of precocious and delayed puberty. Future studies with larger and more diverse cohorts will undoubtedly identify additional genes that affect pubertal timing. The next challenge will be to determine precisely how these genes and pathways regulate pubertal timing so we can better understand the physiology underlying growth and development and the links to adult disease risks.

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References

1. Day FR, Elks CE, Murray A, et al. Puberty timing associated with diabetes, cardiovascular disease and also diverse health outcomes in men and women: the UK Biobank study. *Sci Rep*. 2015; 5:11208. [PubMed: 26084728]
- **2. Day FR, Thompson DJ, Helgason H, et al. Genomic analyses identify hundreds of variants associated with age at menarche and support a role for puberty timing in cancer risk. *Nat Genet*. 2017; 49(6):834–41. This study is the most recent and largest genome-wide association study of age at menarche in 329,345 women of European ancestry and identified 389 loci associated with pubertal timing. These loci account for approximately 7.4% of the variance in pubertal timing in the population and may be linked with cancer risk. [PubMed: 28436984]

3. Mendle J, Ryan RM, McKone KMP. Age at Menarche, Depression, and Antisocial Behavior in Adulthood. *Pediatrics*. 2018; 141(1) This prospective cohort study showed that the association between earlier pubertal timing and higher rates of depression and antisocial behaviors persist into early-middle adulthood.
4. Parent AS, Teilmann G, Juul A, et al. The timing of normal puberty and the age limits of sexual precocity: variations around the world, secular trends, and changes after migration. *Endocr Rev*. 2003; 24(5):668–93. [PubMed: 14570750]
5. Palmert MR, Hirschhorn JN. Genetic approaches to stature, pubertal timing, and other complex traits. *Mol Genet Metab*. 2003; 80(1–2):1–10. [PubMed: 14567953]
6. Towne B, Czerwinski SA, Demerath EW, et al. Heritability of age at menarche in girls from the Fels Longitudinal Study. *Am J Phys Anthropol*. 2005; 128(1):210–9. [PubMed: 15779076]
7. Gajdos ZK, Butler JL, Henderson KD, et al. Association studies of common variants in 10 hypogonadotropic hypogonadism genes with age at menarche. *J Clin Endocrinol Metab*. 2008; 93(11):4290–8. [PubMed: 18728166]
8. Mendoza N, Moron FJ, Quereda F, et al. A digenic combination of polymorphisms within ESR1 and ESR2 genes are associated with age at menarche in the Spanish population. *Reprod Sci*. 2008; 15(3):305–11. [PubMed: 18421025]
9. Rothenbuhler A, Lotton C, Fradin D. Three common variants of LEP, NPY1R and GPR54 show no association with age at menarche. *Horm Res*. 2009; 71(6):331–5. [PubMed: 19506390]
10. He C, Kraft P, Chasman DI, et al. A large-scale candidate gene association study of age at menarche and age at natural menopause. *Hum Genet*. 2010; 128(5):515–27. [PubMed: 20734064]
11. Lu Y, Liu P, Recker RR, et al. TNFRSF11A and TNFSF11 are associated with age at menarche and natural menopause in white women. *Menopause*. 2010; 17(5):1048–54. [PubMed: 20531232]
12. Silva IV, Rezende LC, Lanes SP, et al. Evaluation of PvuII and XbaI polymorphisms in the estrogen receptor alpha gene (ESR1) in relation to menstrual cycle timing and reproductive parameters in post-menopausal women. *Maturitas*. 2010; 67(4):363–7. [PubMed: 20884142]
13. Taylor KC, Small CM, Epstein MP, et al. Associations of progesterone receptor polymorphisms with age at menarche and menstrual cycle length. *Horm Res Paediatr*. 2010; 74(6):421–7. [PubMed: 20814185]
14. Xita N, Chatzikyriakidou A, Stavrou I, et al. The (TTTA)_n polymorphism of aromatase (CYP19) gene is associated with age at menarche. *Hum Reprod*. 2010; 25(12):3129–33. [PubMed: 20937744]
15. Cerne JZ, Pohar-Perme M, Cerkovnik P, et al. Age at menarche and menopause is not associated with two common genetic variants in the methylenetetrahydrofolate reductase (MTHFR) gene. *Eur J Contracept Reprod Health Care*. 2011; 16(4):241–7. [PubMed: 21506883]
16. Riestra P, Garcia-Anguita A, Torres-Cantero A, et al. Association of the Q223R polymorphism with age at menarche in the leptin receptor gene in humans. *Biol Reprod*. 2011; 84(4):752–5. [PubMed: 21159927]
17. Pan R, Liu YZ, Deng HW, et al. Association analyses suggest the effects of RANK and RANKL on age at menarche in Chinese women. *Climacteric*. 2012; 15(1):75–81. [PubMed: 22023082]
18. Xiao W, Ke Y, He J, et al. Association of ALOX12 and ALOX15 gene polymorphisms with age at menarche and natural menopause in Chinese women. *Menopause*. 2012; 19(9):1029–36. [PubMed: 22668814]
19. He C, Murabito JM. Genome-wide association studies of age at menarche and age at natural menopause. *Mol Cell Endocrinol*. 2014; 382(1):767–79. [PubMed: 22613007]
20. Warren Andersen S, Trentham-Dietz A, Gangnon RE, et al. Breast cancer susceptibility loci in association with age at menarche, age at natural menopause and the reproductive lifespan. *Cancer Epidemiol*. 2014; 38(1):62–5. [PubMed: 24373701]
21. Bellini G, Grandone A, Torella M, et al. The Cannabinoid Receptor 2 Q63R Variant Modulates the Relationship between Childhood Obesity and Age at Menarche. *PLoS One*. 2015; 10(10):e0140142. [PubMed: 26447698]
22. Duan P, Wang ZM, Liu J, et al. Gene polymorphisms in RANKL/RANK/OPG pathway are associated with ages at menarche and natural menopause in Chinese women. *BMC Womens Health*. 2015; 15:32. [PubMed: 25884698]

23. He C, Kraft P, Chen C, et al. Genome-wide association studies identify loci associated with age at menarche and age at natural menopause. *Nat Genet.* 2009; 41(6):724–8. [PubMed: 19448621]
24. Ong KK, Elks CE, Li S, et al. Genetic variation in LIN28B is associated with the timing of puberty. *Nat Genet.* 2009; 41(6):729–33. [PubMed: 19448623]
25. Perry JR, Stolk L, Franceschini N, et al. Meta-analysis of genome-wide association data identifies two loci influencing age at menarche. *Nat Genet.* 2009; 41(6):648–50. [PubMed: 19448620]
26. Sulem P, Gudbjartsson DF, Rafnar T, et al. Genome-wide association study identifies sequence variants on 6q21 associated with age at menarche. *Nat Genet.* 2009; 41(6):734–8. [PubMed: 19448622]
27. Elks CE, Perry JR, Sulem P, et al. Thirty new loci for age at menarche identified by a meta-analysis of genome-wide association studies. *Nat Genet.* 2010; 42(12):1077–85. [PubMed: 21102462]
28. Chen CT, Fernandez-Rhodes L, Brzycki RG, et al. Replication of loci influencing ages at menarche and menopause in Hispanic women: the Women's Health Initiative SHARe Study. *Hum Mol Genet.* 2012; 21(6):1419–32. [PubMed: 22131368]
29. Demerath EW, Liu CT, Franceschini N, et al. Genome-wide association study of age at menarche in African-American women. *Hum Mol Genet.* 2013; 22(16):3329–46. [PubMed: 23599027]
30. Spencer KL, Malinowski J, Carty CL, et al. Genetic variation and reproductive timing: African American women from the Population Architecture using Genomics and Epidemiology (PAGE) Study. *PLoS One.* 2013; 8(2):e55258. [PubMed: 23424626]
31. Tanikawa C, Okada Y, Takahashi A, et al. Genome wide association study of age at menarche in the Japanese population. *PLoS One.* 2013; 8(5):e63821. [PubMed: 23667675]
32. Cousminer DL, Stergiakouli E, Berry DJ, et al. Genome-wide association study of sexual maturation in males and females highlights a role for body mass and menarche loci in male puberty. *Hum Mol Genet.* 2014; 23(16):4452–64. [PubMed: 24770850]
33. Perry JR, Day F, Elks CE, et al. Parent-of-origin-specific allelic associations among 106 genomic loci for age at menarche. *Nature.* 2014; 514(7520):92–7. [PubMed: 25231870]
34. Pyun JA, Kim S, Cho NH, et al. Genome-wide association studies and epistasis analyses of candidate genes related to age at menarche and age at natural menopause in a Korean population. *Menopause.* 2014; 21(5):522–9. [PubMed: 24045676]
35. Day FR, Bulik-Sullivan B, Hinds DA, et al. Shared genetic aetiology of puberty timing between sexes and with health-related outcomes. *Nat Commun.* 2015; 6:8842. [PubMed: 26548314]
- *36. Shi J, Zhang B, Choi JY, et al. Age at menarche and age at natural menopause in East Asian women: a genome-wide association study. *Age (Dordr).* 2016; 38(5–6):513–23. This genome-wide association study of age of menarche in 8,073 women of East Asian descent demonstrated overlap with some loci previously identified in women of European ancestry. [PubMed: 27629107]
37. Cousminer DL, Widen E, Palmert MR. The genetics of pubertal timing in the general population: recent advances and evidence for sex-specificity. *Curr Opin Endocrinol Diabetes Obes.* 2016; 23(1):57–65. [PubMed: 26574646]
38. Latronico AC, Brito VN, Carel JC. Causes, diagnosis, and treatment of central precocious puberty. *Lancet Diabetes Endocrinol.* 2016; 4(3):265–74. [PubMed: 26852255]
39. Wei C, Crowne EC. Recent advances in the understanding and management of delayed puberty. *Arch Dis Child.* 2016; 101(5):481–8. [PubMed: 26353794]
40. Croteau-Chonka DC, Lange LA, Lee NR, et al. Replication of LIN28B SNP association with age of menarche in young Filipino women. *Pediatr Obes.* 2013; 8(5):e50–3. [PubMed: 23740805]
41. Delahanty RJ, Beeghly-Fadiel A, Long JR, et al. Evaluation of GWAS-identified genetic variants for age at menarche among Chinese women. *Hum Reprod.* 2013; 28(4):1135–43. [PubMed: 23406970]
42. Carty CL, Spencer KL, Setiawan VW, et al. Replication of genetic loci for ages at menarche and menopause in the multi-ethnic Population Architecture using Genomics and Epidemiology (PAGE) study. *Hum Reprod.* 2013; 28(6):1695–706. [PubMed: 23508249]
43. Hagen CP, Sorensen K, Aksglaede L, et al. Pubertal onset in girls is strongly influenced by genetic variation affecting FSH action. *Sci Rep.* 2014; 4:6412. [PubMed: 25231187]

- *44. Busch AS, Hagen CP, Main KM, et al. Genetic Variation of Follicle-Stimulating Hormone Action Is Associated With Age at Testicular Growth in Boys. *J Clin Endocrinol Metab.* 2017; 102(5): 1740–9. This study demonstrated an association between variants in *FSHB* and *FSHR* and age at testicular enlargement in two ethnically distinct populations of boys. [PubMed: 28323923]
- **45. Busch AS, Hagen CP, Assens M, et al. Differential Impact of Genetic Loci on Age at Thelarche and Menarche in Healthy Girls. *J Clin Endocrinol Metab.* 2018; 103(1):228–34. This article assessed the effects of genetic variants in select genes on two pubertal milestones, age at thelarche and age at menarche, in 1,478 girls and demonstrated that some genetic loci appear to have different effects on thelarche and menarche. [PubMed: 29077908]
46. Chang M, He L, Cai L. An Overview of Genome-Wide Association Studies. *Methods Mol Biol.* 2018; 1754:97–108. This article reviews the role of genome-wide association studies in genetic investigations of complex diseases and traits and provides methodology guidelines. [PubMed: 29536439]
47. Liu YZ, Li J, Pan R, et al. Genome-wide copy number variation association analyses for age at menarche. *J Clin Endocrinol Metab.* 2012; 97(11):E2133–9. [PubMed: 22904172]
48. Lomniczi A, Ojeda SR. The Emerging Role of Epigenetics in the Regulation of Female Puberty. *Endocr Dev.* 2016; 29:1–16. [PubMed: 26680569]
49. Demetriou CA, Chen J, Polidoro S, et al. Methylome analysis and epigenetic changes associated with menarcheal age. *PLoS One.* 2013; 8(11):e79391. [PubMed: 24278132]
50. Binder AM, Corvalan C, Mericq V, et al. Faster ticking rate of the epigenetic clock is associated with faster pubertal development in girls. *Epigenetics.* 2018; 13(1):85–94. [PubMed: 29235933]
51. Abreu AP, Macedo DB, Brito VN, et al. A new pathway in the control of the initiation of puberty: the *MKRN3* gene. *J Mol Endocrinol.* 2015; 54(3):R131–9. [PubMed: 25957321]
52. Lee HS, Jin HS, Shim YS, et al. Low Frequency of *MKRN3* Mutations in Central Precocious Puberty Among Korean Girls. *Horm Metab Res.* 2016; 48(2):118–22. [PubMed: 25938887]
53. Grandone A, Capristo C, Cirillo G, et al. Molecular Screening of *MKRN3*, *DLK1*, and *KCNK9* Genes in Girls with Idiopathic Central Precocious Puberty. *Horm Res Paediatr.* 2017; 88(3–4): 194–200. This study of 60 girls with central precocious puberty described three cases with mutations in *MKRN3*, but did not identify any individuals with mutations in *DLK1* or *KCNK9*. [PubMed: 28672280]
- *54. Dimitrova-Mladenova MS, Stefanova EM, Glushkova M, et al. Males with Paternally Inherited *MKRN3* Mutations May Be Asymptomatic. *J Pediatr.* 2016; 179:263–5. This case series of 10 girls with central precocious puberty and their families reported that male carriers of *MKRN3* mutations may be asymptomatic. [PubMed: 27640350]
55. Neocleous V, Shammass C, Phelan MM, et al. In silico analysis of a novel *MKRN3* missense mutation in familial central precocious puberty. *Clin Endocrinol (Oxf).* 2016; 84(1):80–4. [PubMed: 26173472]
56. Lin WD, Wang CH, Tsai FJ. Genetic screening of the makorin ring finger 3 gene in girls with idiopathic central precocious puberty. *Clin Chem Lab Med.* 2016; 54(3):e93–6. [PubMed: 26402883]
57. Abreu AP, Dauber A, Macedo DB, et al. Central precocious puberty caused by mutations in the imprinted gene *MKRN3*. *N Engl J Med.* 2013; 368(26):2467–75. [PubMed: 23738509]
58. Schreiner F, Gohlke B, Hamm M, et al. *MKRN3* mutations in familial central precocious puberty. *Horm Res Paediatr.* 2014; 82(2):122–6. [PubMed: 25011910]
59. Simon D, Ba I, Mekhail N, et al. Mutations in the maternally imprinted gene *MKRN3* are common in familial central precocious puberty. *Eur J Endocrinol.* 2016; 174(1):1–8. [PubMed: 26431553]
60. Macedo DB, Abreu AP, Reis AC, et al. Central precocious puberty that appears to be sporadic caused by paternally inherited mutations in the imprinted gene makorin ring finger 3. *J Clin Endocrinol Metab.* 2014; 99(6):E1097–103. [PubMed: 24628548]
- *61. Bessa DS, Macedo DB, Brito VN, et al. High Frequency of *MKRN3* Mutations in Male Central Precocious Puberty Previously Classified as Idiopathic. *Neuroendocrinology.* 2017; 105(1):17–25. This study of 20 boys with central precocious puberty was the first to report the frequency of *MKRN3* mutations in boys, which was higher than that previously reported in girls with central precocious puberty. [PubMed: 27225315]

62. Christoforidis A, Skordis N, Fanis P, et al. A novel MKRN3 nonsense mutation causing familial central precocious puberty. *Endocrine*. 2017; 56(2):446–9. This article reports a novel nonsense mutation in the *MKRN3* gene in a family with multiple affected members with central precocious puberty. [PubMed: 28132164]
- *63. Liu H, Kong X, Chen F. Mkrn3 functions as a novel ubiquitin E3 ligase to inhibit Nptx1 during puberty initiation. *Oncotarget*. 2017; 8(49):85102–9. This study provided evidence from mice that Mkrn3 functions as a ubiquitin E3 ligase, possibly within the hypothalamus. [PubMed: 29156706]
64. Macedo DB, Silveira LF, Bessa DS, et al. Sexual Precocity--Genetic Bases of Central Precocious Puberty and Autonomous Gonadal Activation. *Endocr Dev*. 2016; 29:50–71. [PubMed: 26680572]
65. Day FR, Perry JR, Ong KK. Genetic Regulation of Puberty Timing in Humans. *Neuroendocrinology*. 2015; 102(4):247–55. [PubMed: 25968239]
- **66. Dauber A, Cunha-Silva M, Macedo DB, et al. Paternally Inherited DLK1 Deletion Associated With Familial Central Precocious Puberty. *J Clin Endocrinol Metab*. 2017; 102(5):1557–67. This study associated a genetic defect in *DLK1* with central precocious puberty in a large, multigenerational family with multiple affected members. [PubMed: 28324015]
67. Ioannides Y, Lokulo-Sodiye K, Mackay DJ, et al. Temple syndrome: improving the recognition of an underdiagnosed chromosome 14 imprinting disorder: an analysis of 51 published cases. *J Med Genet*. 2014; 51(8):495–501. [PubMed: 24891339]
68. Jung J, Mo JS, Kim MY, et al. Regulation of Notch1 signaling by Delta-like ligand 1 intracellular domain through physical interaction. *Mol Cells*. 2011; 32(2):161–5. [PubMed: 21643850]
69. Biehl MJ, Raetzman LT. Rbpj-kappa mediated Notch signaling plays a critical role in development of hypothalamic Kisspeptin neurons. *Dev Biol*. 2015; 406(2):235–46. [PubMed: 26318021]
- *70. Leka-Emiri S, Chrousos GP, Kanaka-Gantenbein C. The mystery of puberty initiation: genetics and epigenetics of idiopathic central precocious puberty (ICPP). *J Endocrinol Invest*. 2017; 40(8): 789–802. This article reviews the genetics and epigenetics of central precocious puberty and discusses environmental influences on pubertal timing. [PubMed: 28251550]
71. Teles MG, Bianco SD, Brito VN, et al. A GPR54-activating mutation in a patient with central precocious puberty. *N Engl J Med*. 2008; 358(7):709–15. [PubMed: 18272894]
72. Silveira LG, Noel SD, Silveira-Neto AP, et al. Mutations of the KISS1 gene in disorders of puberty. *J Clin Endocrinol Metab*. 2010; 95(5):2276–80. [PubMed: 20237166]
73. Oh YJ, Rhie YJ, Nam HK, et al. Genetic Variations of the KISS1R Gene in Korean Girls with Central Precocious Puberty. *J Korean Med Sci*. 2017; 32(1):108–14. This case-control study of 194 girls with central precocious puberty suggested that two common variants in *KISS1R* may be associated with central precocious puberty. [PubMed: 27914139]
74. Chou IC, Wang CH, Lin WD, et al. Association study in Taiwanese girls with precocious puberty. *J Pediatr Endocrinol Metab*. 2011; 24(1–2):103–4. [PubMed: 21528826]
75. Silveira-Neto AP, Leal LF, Emerman AB, et al. Absence of functional LIN28B mutations in a large cohort of patients with idiopathic central precocious puberty. *Horm Res Paediatr*. 2012; 78(3):144–50. [PubMed: 22964795]
76. Hu Z, Chen R, Cai C. Association of genetic polymorphisms around the LIN28B gene and idiopathic central precocious puberty risks among Chinese girls. *Pediatr Res*. 2016; 80(4):521–5. This case-control study of 502 girls with central precocious puberty suggested that two common variants in *LIN28B* may be associated with central precocious puberty. [PubMed: 27304100]
77. Krstevska-Konstantinova M, Tasic VB, Montenegro LR, et al. Mutational analysis of TAC and TACR3 in idiopathic central precocious puberty. *Pril (Makedon Akad Nauk Umet Odd Med Nauki)*. 2014; 35(1):129–32. [PubMed: 24802197]
78. Xin X, Zhang J, Chang Y, et al. Association study of TAC3 and TACR3 gene polymorphisms with idiopathic precocious puberty in Chinese girls. *J Pediatr Endocrinol Metab*. 2015; 28(1–2):65–71. [PubMed: 25153567]
79. Luo Y, Liu Q, Lei X, et al. Association of estrogen receptor gene polymorphisms with human precocious puberty: a systematic review and meta-analysis. *Gynecol Endocrinol*. 2015; 31(7):516–21. [PubMed: 26036718]

80. Zhao Y, Chen T, Zhou Y, et al. An association study between the genetic polymorphisms within GnRHI, LHbeta and FSHbeta genes and central precocious puberty in Chinese girls. *Neurosci Lett.* 2010; 486(3):188–92. [PubMed: 20869425]
81. Cukier P, Wright H, Rulfs T, et al. Molecular and gene network analysis of thyroid transcription factor 1 (TTF1) and enhanced at puberty (EAP1) genes in patients with GnRH-dependent pubertal disorders. *Horm Res Paediatr.* 2013; 80(4):257–66. [PubMed: 24051510]
82. Lima CJ, Cardoso SC, Lemos EF, et al. Mutational analysis of the genes encoding RFamide-related peptide-3, the human orthologue of gonadotrophin-inhibitory hormone, and its receptor (GPR147) in patients with gonadotrophin-releasing hormone-dependent pubertal disorders. *J Neuroendocrinol.* 2014; 26(11):817–24. [PubMed: 25180599]
83. Lee HS, Kim KH, Hwang JS. Association of aromatase (TTTA)n repeat polymorphisms with central precocious puberty in girls. *Clin Endocrinol (Oxf).* 2014; 81(3):395–400. [PubMed: 24612204]
84. Matsuzaki CN, Junior JM, Damiani D, et al. Are CYP11A1, CYP17 and CYP11B1 mutation genes involved on girls with precocious puberty? A pilot study. *Eur J Obstet Gynecol Reprod Biol.* 2014; 181:140–4. [PubMed: 25150952]
85. Palmert MR, Dunkel L. Clinical practice. Delayed puberty. *N Engl J Med.* 2012; 366(5):443–53. [PubMed: 22296078]
86. Topaloglu AK. Update on the Genetics of Idiopathic Hypogonadotropic Hypogonadism. *J Clin Res Pediatr Endocrinol.* 2017; 9(Suppl 2):113–22. This article reviews recent advancements in the genetics of idiopathic hypogonadotropic hypogonadism. [PubMed: 29280744]
87. Sidhoum VF, Chan YM, Lippincott MF, et al. Reversal and relapse of hypogonadotropic hypogonadism: resilience and fragility of the reproductive neuroendocrine system. *J Clin Endocrinol Metab.* 2014; 99(3):861–70. [PubMed: 24423288]
88. Howard SR, Guasti L, Ruiz-Babot G, et al. IGSF10 mutations dysregulate gonadotropin-releasing hormone neuronal migration resulting in delayed puberty. *EMBO Mol Med.* 2016; 8(6):626–42. [PubMed: 27137492]
- *89. Cassatella D, Howard S, Acierno J, et al. Congenital Hypogonadotropic Hypogonadism and Constitutional Delay of Growth and Puberty Have Distinct Genetic Architectures. *Eur J Endocrinol.* 2018 In contrast to a previous study, this study in 72 individuals with delayed puberty did not identify an enrichment of mutations in a panel of 24 genes implicated in idiopathic hypogonadotropic hypogonadism compared to controls.
90. Beneduzzi D, Trarbach EB, Min L, et al. Role of gonadotropin-releasing hormone receptor mutations in patients with a wide spectrum of pubertal delay. *Fertil Steril.* 2014; 102(3):838–46 e2. [PubMed: 25016926]
91. Vaaralahti K, Wehkalampi K, Tommiska J, et al. The role of gene defects underlying isolated hypogonadotropic hypogonadism in patients with constitutional delay of growth and puberty. *Fertil Steril.* 2011; 95(8):2756–8. [PubMed: 21292259]
92. Tusset C, Noel SD, Trarbach EB, et al. Mutational analysis of TAC3 and TACR3 genes in patients with idiopathic central pubertal disorders. *Arq Bras Endocrinol Metabol.* 2012; 56(9):646–52. [PubMed: 23329188]
93. Zhu J, Choa RE, Guo MH, et al. A shared genetic basis for self-limited delayed puberty and idiopathic hypogonadotropic hypogonadism. *J Clin Endocrinol Metab.* 2015; 100(4):E646–54. [PubMed: 25636053]
94. Banerjee I, Trueman JA, Hall CM, et al. Phenotypic variation in constitutional delay of growth and puberty: relationship to specific leptin and leptin receptor gene polymorphisms. *Eur J Endocrinol.* 2006; 155(1):121–6. [PubMed: 16793957]
95. Murray PG, Read A, Banerjee I, et al. Reduced appetite and body mass index with delayed puberty in a mother and son: association with a rare novel sequence variant in the leptin gene. *Eur J Endocrinol.* 2011; 164(4):521–7. [PubMed: 21296922]
96. Joustra SD, Wehkalampi K, Oostdijk W, et al. IGSF1 variants in boys with familial delayed puberty. *Eur J Pediatr.* 2015; 174(5):687–92. [PubMed: 25354429]

97. Banerjee I, Hanson D, Perveen R, et al. Constitutional delay of growth and puberty is not commonly associated with mutations in the acid labile subunit gene. *Eur J Endocrinol.* 2008; 158(4):473–7. [PubMed: 18362293]
98. Pugliese-Pires PN, Fortin JP, Arthur T, et al. Novel inactivating mutations in the GH secretagogue receptor gene in patients with constitutional delay of growth and puberty. *Eur J Endocrinol.* 2011; 165(2):233–41. [PubMed: 21646290]
99. Tommiska J, Wehkalampi K, Vaaralahti K, et al. LIN28B in constitutional delay of growth and puberty. *J Clin Endocrinol Metab.* 2010; 95(6):3063–6. [PubMed: 20350940]
100. Styne DM, Grumbach MM. Physiology and Disorders of Puberty. In: Kronenberg HM, Larsen PR, Melmed S, Polonsky KS, editors *Williams Textbook of Endocrinology*. 13. Philadelphia, PA: Elsevier; 2016. 1074–218.
101. Bordini B, Rosenfield RL. Normal pubertal development: Part I: The endocrine basis of puberty. *Pediatr Rev.* 2011; 32(6):223–9. [PubMed: 21632873]
102. Bordini B, Rosenfield RL. Normal pubertal development: part II: clinical aspects of puberty. *Pediatr Rev.* 2011; 32(7):281–92. [PubMed: 21724902]

KEY POINTS

- Genome-wide association studies have identified hundreds of common genetic loci that affect normal pubertal timing in both sexes and across ethnic groups. Several of these loci have also been implicated in precocious and delayed puberty. Some loci may preferentially impact certain pubertal milestones but not others.
- The first single-gene causes of precocious puberty (*MKRN3*, *DLK1*) and delayed puberty (*IGSF10*) are being characterized.
- Mechanisms for how these genetic loci influence pubertal timing may include effects on the development and function of GnRH neurons, their activation at the time of puberty, and the responsiveness of end-organs.

Figure 1. (Original) Putative sites of action for genes implicated in precocious puberty, normal variation in pubertal timing, and delayed puberty
Select genes are listed next to their likely sites of action within the hypothalamic-pituitary-gonadal axis. Of note, some genes implicated in precocious puberty (*DLK1*, *MKRN3*, and *KISS1*) and in delayed puberty (*TACR3*) are also associated with variation in normal pubertal timing, indicated by underlining.

Figure 2. (Original) Potential mechanisms underlying variation in pubertal timing

The graph schematizes the hormonal and physical events that mark pubertal onset and shows potential mechanisms for variation in pubertal timing. The solid black curve in panel A represents typical hormone production over time, with a period of robust activity in infancy (“minipuberty”), a relative quiescence in childhood, and reemergence of activity at puberty. The dashed line represents the “threshold” concentration of gonadotropins and/or sex-steroids needed for the appearance of physical signs of puberty, such as testicular growth in males and thelarche in females. These physical signs appear when hormonal activity reaches the threshold, indicated by the circle.

Three potential mechanisms for variation in pubertal timing are illustrated in Panels B–D. The solid black curve depicts normal pubertal timing. Variations resulting in differences in pubertal timing are depicted in gray; these include variation in the timing of activation of the GnRH neuronal network (B), in the rate of rise of gonadotropins/sex-steroids (C), and in end organ responsiveness to gonadotropins and/or sex steroids (D). These mechanisms are not mutually exclusive.

Table 1

(Original) Genome-Wide Association Studies on Pubertal Timing

Study [Reference]	Year	Ancestry of Study Population	Number of Individuals in Primary Analysis	Number of Individuals in Replication Analysis	Pubertal Marker Studied	Number of Genome-Wide Significant Loci Identified	% of Population Variance Explained
He et al. [23]	2009	European	17,438 women	—	Menarche	10	0.6
Ong et al. [24]	2009	European	4,714 women	16,373	Menarche	1	0.2
Perry et al. [25]	2009	European	17,510 women	—	Menarche	2	—
Sulem et al. [26]	2009	European	15,297 women	10,040	Menarche	5	—
Elks et al. [27]	2010	European	87,802 women	14,731	Menarche	32	1.3
Chen et al. [28]	2012	Hispanic	3,468 women	—	Menarche	0	—
Demerath et al. [29]	2013	African American	18,089 women	2,850	Menarche	0	—
Spencer et al. [30]	2013	African American	4,159 women	—	Menarche	0	—
Tanikawa et al. [31]	2013	Japanese	15,495 women	—	Menarche	0	—
Cousminer et al. [32]	2014	European	6,147 girls	—	Breast Tanner Stage	1	—
		European	3,769 boys	—	Genital Tanner Stage	1	—
Perry et al. [33]	2014	European	182,416 women	8,689	Menarche	106	2.7
Pyun et al. [34]	2014	Korean	3,437 women	—	Menarche	0	—
Day et al. [35]	2015	European	55,871 men	—	Voice Breaking	9	—
Shi et al. [36*]	2016	Chinese	8,073 women	8,322	Menarche	0	—
Day et al. [2**]	2017	European	329,345 women	39,543	Menarche	389	7.4