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Genetic Determinants of Pubertal Timing in the General Population

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Abstract

Puberty is an important developmental stage during which reproductive capacity is attained. The timing of puberty varies greatly among healthy individuals in the general population and is influenced by both genetic and environmental factors. Although genetic variation is known to influence the normal spectrum of pubertal timing, the specific genes involved remain largely unknown. Genetic analyses have identified a number of genes responsible for rare disorders of pubertal timing such as hypogonadotropic hypogonadism and Kallmann syndrome. Recently, the first loci with common variation reproducibly associated with population variation in the timing of puberty were identified at 6q21 in or near *LIN28B* and at 9q31.2. However, these two loci explain only a small fraction of the genetic contribution to population variation in pubertal timing, suggesting the need to continue to consider other loci and other types of variants. Here we provide an update of the genes implicated in disorders of puberty, discuss genes and pathways that may be involved in the timing of normal puberty, and suggest additional avenues of investigation to identify genetic regulators of puberty in the general population.

Keywords

puberty; pubertal timing; genetics; hypogonadotropic hypgonadism; Kallmann syndrome; genetic regulation

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Introduction

The timing of puberty varies greatly in the general population and is influenced by both genetic and environmental factors [reviewed in [1–6]]. The high correlation of the onset of puberty seen within racial/ethnic groups, within families, and between monozygotic compared to dizygotic twins all provide evidence for genetic regulation of pubertal timing. Taken together, these data suggest that 50–80% of the variation in pubertal timing is determined by genetic factors [1,3–10]. Environmental and physiologic effects also influence the timing of puberty, and there is evidence supporting secular trends in the timing of puberty [1,11–13]. It is possible that gene by environment interactions play an important role in regulating the timing of puberty. However, despite changing environmental and secular influences, genetic background still plays a significant role in regulating the variation of pubertal timing within a population at any particular point in time. Thus, while acknowledging the importance of environmental factors, in this review we highlight the use of genetic methodologies to investigate the regulation of pubertal timing.

Much progress has been made in identifying genetic causes of disorders of puberty, such as hypogonadotropic hypogonadism (HH) and Kallmann syndrome (KS), but the specific genetic factors that regulate the variation in pubertal timing in the general population are just emerging. The identification of these genes has been difficult because pubertal timing is a complex genetic trait, where a direct, often one-to-one relationship between genotype and phenotype does not exist [14], likely due to multigenic influences and interactions between genetic variants and environmental exposures [15].

Insights from Single Gene Disorders

Investigation of HH and KS has led to the identification of many genes that play critical roles in the development and regulation of the hypothalamic pituitary gonadal (HPG) axis (reviewed in [4,16–20]). For example, this work has defined roles for the genes that lead to HH (*GNRHR*, *GNRH1*, *GPR54*, *FGFR1*, *FGF8*, *PROK2*, *PROKR2*, *TAC3*, *TACR3*, and *CHD7*), to X-linked (*KAL1*) and autosomal (*FGFR1*, *PROK2*, *PROKR2*, *FGF8*, and *CHD7*) forms of KS, to obesity and HH (*LEP*, *LEPR*, and *PC1*), and to abnormal HPG development (*DAX1*, *SF-1*, *HESX-1*, *LHX3*, and *PROP-1*).

Genetic causes of other disorders of pubertal development, such as precocious puberty, have been previously reviewed [18,21]. In this review, we focus on discussion of genes that are hypothesized to regulate pubertal timing at the hypothalamic level.

Normosmic hypogonadotropic hypogonadism

HH with normal olfaction has been primarily associated with mutations in the genes for the gonadotropin-releasing hormone receptor (*GNRHR)* and the G-protein coupled receptor 54 (*GPR54),* the G-protein coupled receptor for kisspeptins (the products of *KISS1*) [22–30]. Estimates of the frequency of *GNRHR* mutations in normosmic HH range from 3.5–10.4% [31,32]. Recently, mutations in *GNRH1* were also identified in patients with normosmic HH [33,34]. A case of constitutional delay of growth and puberty (CDGP) was reportedly associated with a homozygous partial loss of function mutation in *GNRHR* [35], and pedigrees of probands with HH can include individuals with delayed but otherwise normal puberty. However, more extensive analyses suggest that genetic variation in neither *GNRH* nor *GNRHR* is a common cause of late puberty in the general population [36,37].

Research into the KISS-1/GPR54 system in both animal and human studies has identified it as a critical component of the HPG axis, necessary for pubertal onset. The first indications

of the importance of the KISS-1/GPR54 signaling complex as a regulator of the HPG axis came in 2003 when two independent groups reported deletions and inactivating mutations of *GPR54* in patients with HH [23,25]. Subsequently, activating mutations in this pathway were associated with precocious puberty in a report of central precocious puberty in the case of a female with an autosomal dominant mutation in *GPR54* [38]. Thus, it is clear that activation of GPR54 by kisspeptins plays a pivotal role in the onset of puberty. It is not yet known, however, whether the KISS-1/GPR54 system is the initial trigger of puberty or whether it acts as a downstream effector of other yet to be identified regulatory factors [39,40]. Recently, mutations in *TAC3* and *TACR3* were identified in HH patients [41]. These genes encode neurokinin B and its receptor, which are highly expressed in the same neurons that express kisspeptin, further emphasizing the role of kisspeptin in the regulation of pubertal timing.

Kallmann syndrome

Several genes critical to HPG axis function and olfactory development have been identified through investigation of Kallmann syndrome (hypogonadotropic hypogonadism with anosmia/hyposmia). Mutations in Kallmann syndrome 1 (*KAL-1)* [42–44] and fibroblast growth factor receptor 1 (*FGFR1)* [45] have been implicated in the X-linked and autosomal dominant forms of the disease, respectively, but appear to account for only approximately 20% of patients with KS [46]. Recently, mutations in the prokineticin receptor-2 gene (*PROKR2)*, a G-protein coupled receptor, and in its ligand prokinetcin-2 *(PROK2)* were identified in a cohort of KS patients [46], demonstrating that prokineticin signaling is important for olfactory and HPG axis development. One of the patients in this series was heterozygous for both a *PROKR2* mutation and a *KAL1* mutation, suggesting a possible digenic mode of inheritance [46]. Finally, mutations in the nasal embryonic luteinizing hormone releasing hormone factor (*NELF*), which plays a role in migration of GnRH neurons and olfactory axon outgrowth [47], have also been implicated in the pathogenesis of KS [48]. A heterozygous deletion in *NELF* has been reported as a component, along with *FGFR1*, of digenic KS, but it is not clear whether mutations in *NELF* alone lead to KS [49].

The distinction among the different abnormalities of pubertal development may not be absolute. For example, mutations in *FGFR1* can cause both KS and HH [50], and a homozygous mutation in *PROK2* has been reported to cause both KS and HH within a single kindred [51]. A more comprehensive study of *PROK2* and *PROKR2* in HH and KS patients found mutations in both genes distributed in both groups of patients [52]. Mutations in the *FGF8* gene, which encodes a ligand for *FGFR1*, have been observed in HH patients accompanied by variable olfactory phenotypes [53]. Recently, mutations in *CHD7*, a gene responsible for CHARGE syndrome, which shares some developmental features with KS, were identified in patients with both normosmic HH and KS [54,55]. Moreover, it has been reported that loss of function mutations in *FGFR1* can cause delayed puberty in members of HH pedigrees [50,56], although variation in *FGFR1* does not appear to be a major cause of CDGP [37]. Cases of reversible HH have also been reported [57], further blurring the distinction between HH and CDGP.

Leptin and other genes

HH (accompanied by obesity) can also result from defects in the leptin (*LEP*) or the leptin receptor (*LEPR*) genes, highlighting the importance of nutrition in modulating the HPG axis. Leptin appears to act as a permissive factor in pubertal maturation [5]. However, recent association studies have found no substantial association between common polymorphisms in *LEP* and *LEPR* and CDGP or age at menarche in the general population [37,58].

Other causes of HH include mutations in genes that are critical to HPG development. This category includes the genes for the orphan nuclear receptors *DAX1* (dosage-sensitive sex reversal adrenal hypoplasia critical (DSS-AHC) region on the X chromosome, gene 1) and steroidogenic factor-1 (*SF-1*). Mutations in several pituitary transcription factors, including *HESX-1*, *LHX3*, and *PROP1*, can lead to combined pituitary hormone deficiencies that include HH as a phenotype. Finally, the gene for prohormone convertase-1 (*PC-1*) has been associated with obesity and HH, possibly as a result of defective processing of neuropeptides or prohormones that are components of GnRH secretion [20,59].

Genetic Variation in Normal Puberty

Candidate gene-based association studies

The most commonly used approach for identifying the variants that affect the timing of puberty in the general population has been candidate gene-based association studies. Such studies typically involve genotyping a panel of common variants, usually single nucleotide polymorphisms (SNPs), and determining if the frequency of any of the variants is correlated in a statistically significant manner with phenotype. Because it is clear that the information gained from the study of HH and KS is critical to our understanding of the reproductive-endocrine axis, the genes and pathways identified in these disorders provide attractive candidate genes for association studies investigating variation in pubertal timing within the general population. In many instances, SNPs in the same genes that cause monogenic forms of a phenotype or disease have been associated with the corresponding common, complex trait, and it is possible that this could be the case for puberty as well [60–64]. A substantial fraction of loci associated with traits such as obesity, height, type 2 diabetes, and lipid levels include genes that are mutated in related monogenic disorders [65]. Other disorders of pubertal timing such as CDGP, which likely represents the extreme end of normal pubertal timing, and idiopathic central precocious puberty have significant genetic components as well and may represent additional sources of candidate genes as more genes that cause these conditions are identified [66–72], [73]. This paradigm is illustrated in Figure 1, which depicts what is known and unknown about the overlap among the genetic causes of the different categories of delayed puberty, highlighting the need to study HH genes in the general population.

In a recent study, we used association studies to test for associations between common variants in ten HH-related genes (*GNRH*, *GNRHR*, *GPR54*, *KISS1*, *LEP*, *LEPR*, *FGFR1*, *KAL1*, *PROK2*, and *PROKR2*) and age at menarche. However, only nominally significant associations between SNPs in several of the genes and age at menarche were identified, indicating that genetic variation in these ten genes does not appear to be a substantial modulator of pubertal timing in the general population [37]. Other work has also shown no evidence for substantial association between SNPs in *GNRH* and *GNRHR* [36] or *LEP* and *LEPR* [58] and alterations in pubertal timing. Variation near these genes but outside the regions typically studied in candidate gene association studies could still influence population variation in the timing of puberty, as is the case for a common variant near *MC4R* and obesity [74]. It is also possible that variants with low effect sizes in or near these genes could play a role in regulating pubertal timing, although such variants would be unlikely to explain much of the observed phenotypic variation and would not negate the need to look elsewhere for variants that influence the timing of puberty. More likely, though, is that unless other genes, or combinations of genes, in these pathways modulate the timing of puberty in the general population, new regulators need to be identified and studied [39,40].

The need to identify new genes and pathways is perhaps not surprising since mutations in known genes are only responsible for about 30% of the cases of HH and KS [18,49]. Indeed,

although there are notable exceptions, most of the genes that have recently been identified through genome-wide association studies as being associated with various complex traits have not been prior candidate genes for the phenotypes in question.

Despite their promise, there are limitations to the approach taken in traditional association studies. Such studies have typically involved relatively small numbers of individuals and may lack the power to identify variants with small effect sizes such as those that have been identified through genome-wide association (GWA) studies [75], particularly when large sample sizes are achieved through collaboration and meta-analysis. Candidate gene association studies also examine only those regions of the genome that directly abut the gene in question, but variants associated with phenotypes may lie outside those regions [74].

Linkage analysis

One approach that does not rely upon candidate genes and that interrogates the whole genome is linkage analysis. These studies are designed to identify regions of the genome [quantitative trait loci (QTLs)] that harbor genes that modulate a specific trait. Linkage studies do not require a priori assumptions about causative genes or pathways and may, therefore, lead to discovery of novel regulatory genes. Several recent studies have used linkage to investigate the genetic basis for variation in age at menarche (AAM) in human populations [76–79], but the results have been somewhat disappointing. As can be seen from inspection of Table 1, none of the findings from the individual studies has been independently replicated, and each study describes QTLs at different genomic locations. Thus, it is possible that the results represent false positives or false negatives and replication is needed before one can conclude that linkage analyses have identified areas of the genome that modulate AAM. The lack of a statistically significant finding in a recent large linkage study [76] that involved more than 13,000 individuals and almost 5,000 sister-pairs suggests that no single QTL explains a large proportion of the variance in AAM.

As a corollary to human studies, investigation using animal models may suggest new lines of investigation for human studies. As one example, a combination of linkage analysis and generation of congenic mouse strains has led to the identification and validation of a statistically significant QTL associated with timing of vaginal opening (a phenotypic marker of puberty in mice) on mouse chromosome 6 in a region that corresponds to human chromosome 12p11–12 [80]. This and other studies [40,81] may eventually provide important clues as to new candidate genes/pathways to investigate in humans.

Genome-wide association (GWA) studies

Over the past two years, great progress has been made using GWA studies to identify genes that affect susceptibility to common diseases and that modulate complex trait phenotypes, such as obesity and height [74,82–86]. GWA studies are particularly powerful because they query SNPs throughout the genome (often testing for association between a particular disease/phenotype and as many as 900,000 SNPs) and because collectively GWA studies have been performed in populations of tens or even hundreds of thousands of individuals. Therefore, these large, often highly collaborative, studies have sufficient power to detect genetic variants with relatively small effects on disease susceptibility/trait phenotype.

Results from the first GWA studies for AAM have now been published, with confirmed associations at two loci, at 6q21 (in or near the *LIN28B* gene) and at 9q31.2 [87–90]. These studies involved between 17,000 and 25,000 individuals all of European descent. In each case, AAM was analyzed but in one study [87] additional phenotypes (breast development in girls, voice breaking and pubic hair development in boys, and tempo of height growth in both boys and girls) were found to associate with variants in *LIN28B*, suggesting that control

of pubertal timing in boys and girls shares some common elements. One study found that the signal at *LIN28B* could be split into two haplotypes, suggesting that either multiple variants may associate with AAM at this locus or that a SNP that has not yet been tested for association may represent the true association signal [88]. Effect sizes were estimated at approximately 1.2 months earlier per effect allele for *LIN28B* [87,90] and 9q31.2 [90]. The two loci together are estimated to explain 0.6% of the variation in AAM [89]. None of the recent GWA studies observed the previously reported association at the *SPOCK* locus [91], suggesting that that reported association may represent a false positive.

It is important to note that although these studies and many of the previously described studies have primarily used recalled AAM for analyses and that recalled AAM is highly correlated with actual AAM [92,93], even when recalled as many as 30 years later [93]. Categorizing AAM and/or using the extremes can both improve the accuracy of recall [93,94]. However, AAM is only one of several events that comprise puberty, and other data should also be used when available. One of the recent large GWA studies found that the same allele that was associated with earlier AAM was also associated with earlier breast development [87], supporting the known correlation between breast development and AAM [95]. Should large cohorts become available with phenotype data for other puberty-related events, they may provide additional insights into the genetics of the timing of puberty and help to determine if different genes modulate different aspects of pubertal development (*i.e*, adrenarche, gonadarche, menarche) [95].

Variation at *LIN28B* has also been associated with adult height, although the effect at this locus on AAM does not appear to be mediated in a simple manner through its effect on adult height [88]. One study found that the allele associated with earlier age at menarche in was associated with reduced adult height in the same samples [90]. More likely, this result demonstrates that the same genetic pathway can regulate both phenotypes. *LIN28B* has two distinct isoforms [96] and encodes a regulator of the let-7 class of microRNAs [97]. *LIN28B* is thought to play an important role in both cell pluripotency and cancer [97], but how this regulatory system modulates growth and the timing of puberty is unknown. The identification of this locus as a regulator of the timing of puberty will likely lead to new biology new understanding about how microRNAs regulate human developmental processes.

The biology behind the locus at 9q31.2 also remains unknown. The associated SNPs lie in an intergenic region with no obvious candidate genes nearby. The closest gene is *TMEM38B*, a transmembrane protein gene, which lies approximately 400kb away from the signal at 9q31.2 [90].

Because AAM has been correlated with both height [98] and body mass index (BMI) [99], and because of the *LIN28B* effects on both height and AAM, several of the recent GWA studies also looked for association of AAM with the known height and BMI loci. One study saw no association between height loci other than *LIN28B* and AAM [88], although another study found that some height loci were nominally significant for association with AAM [90]. Both studies found that many of the BMI loci were associated with AAM, with the BMI increasing allele associated with earlier AAM [88,90]. This finding suggests that increased BMI in childhood may directly decrease AAM, which is an interesting finding given the observed link in population studies between the age at puberty and BMI [99]. An important area of future research will involve investigating the extent to which genes that regulate growth, genes that regulate sex steroid production and response, and genes that regulate the central portion of the HPG axis are distinct or overlapping. As discussed above, there are already some potential hints of overlap, at *LIN28b* (puberty and height) and at several loci previously reported to be associated with BMI (puberty and BMI).

It is a common story in the investigation of many common diseases and complex traits that great progress has derived from the study of monogenic diseases but that less progress has derived from candidate gene approaches and from linkage analysis. In these examples, as with the timing of puberty, GWA studies have been needed to make substantial progress in identifying common genetic variants that modulate disease susceptibility/trait phenotype within the general population. It is also a common experience that the effect sizes of many of the associations identified in GWA studies are relatively small [100]. However, the small effect size does not negate the importance of the discovery. Findings from GWA studies have highlighted biological pathways involved in a variety of phenotypes, both through "rediscovery" of genes known to be important (for example, 11 of 23 associations for lipid traits are in or near key lipid metabolism proteins) and through identifying previously unsuspected pathways (for example, height and chromatin or Crohn's disease and autophagy) [65].

Other approaches

Although the first genetic associations with the timing of puberty are now beginning to emerge, they, as discussed, represent variants with small effect sizes, consistent with findings for other complex traits such as height and obesity [75,101]. This suggests that to understand more fully the genetic variation that influences the timing of puberty, other approaches will be necessary.

Meta-analysis—The first of these will likely involve a meta-analyis of the GWA study data published by the four independent research groups. Such an analysis has the potential to involve more than 100,000 women and will, undoubtedly, identify additional loci that regulate the timing of puberty. However, it is likely that each of these loci has a smaller effect than the loci at *LIN28B* and at 9q32.1. Thus, even after the meta-analysis is performed, additional strategies will be needed to identify the genetic factors that explain 50–80% of the variation in pubertal timing among the general population.

Sequencing—If common variants can explain only a small portion of genetic heritability, it is possible that rare variants explain some of the variation as well. The common variant/common disease hypothesis [102,103] would suggest that common sequence variants (such as SNPs, generally present in ≥ 1% of the population), each exerting a relatively small effect on the phenotype, act in combination to influence the timing of puberty. An alternative, although not mutually exclusive, hypothesis is that larger numbers of rare variants, each present in perhaps ≤ 1 % of the population, exert modest to large individual effects that collectively explain much of the genetic variance in pubertal timing. Current GWA studies have allowed interrogation of SNPs present at ≥ 5% in the population, but newer versions of GWA studies building on data from the 1000 Genomes Project (www.1000genomes.org) will allow investigation of rarer SNPs. One approach that addresses both of these mechanisms is resequencing of candidate genes to determine if sequence variants are present at different frequencies among individuals with early or late pubertal development. We and others are actively investigating the role that sequence variation in genes responsible for HH and KS plays in modulating pubertal timing. For example, we have resequenced the exonic regions of several candidate genes, including *GNRHR, GNRH1, LEP*, *LEPR,* and *FGFR1*, in populations of approximately 50 individuals with late, but otherwise normal pubertal development [36,37,58]. Thus far, no variants have been identified in these genes that explain the variation in pubertal timing within the general population. However, recent studies that used resequencing to identify variants that control triglyceride levels suggest that several hundred to thousands of subjects/DNA samples may be needed to employ this strategy most effectively [104,105].

Alternative genetic mechanisms—In addition to common and rare variants, future investigation of the genetic regulation of pubertal timing should expand to include non-traditional genetic mechanisms. It is possible, for example, that rare, large copy number variants may play a role in regulation of the onset of puberty as they have in susceptibility to diseases such as schizophrenia and cancer [106]. Epigenetic mechanisms have been shown to regulate the timing of puberty and reproductive function in rodents [107], and this is another mechanism that could modulate the timing of puberty in humans and effect gene by environment interactions.

Population Variation in Pubertal Timing

Thus far we have focused our discussion on variation in pubertal timing among individuals, but the timing of the appearance of the different secondary sexual characteristics that typify puberty varies among population groups as well [1]. For example, age at menarche is known to vary among different ethnic groups within the United States [108–114]. Given this, it seems reasonable to hypothesize that there is an association between global genetic ancestry and markers of pubertal timing. To test this hypothesis, we genotyped SNPs that show high variation in frequency in different population groups (ancestry informative markers) to estimate global genetic ancestry and used those estimates to test for an association between genetic ancestry and age at menarche among a sample of participants in the Hawai'i and Los Angeles Multiethnic Cohort. We found significant evidence of association between European ancestry and age at menarche among Latinas, with increased European ancestry and decreased Native American ancestry associated with late menarche, and suggestive evidence of association between Native Hawaiian ancestry and age at menarche in Native Hawaiians, with increased Native Hawaiian ancestry and decreased European and East Asian ancestry associated with early menarche (Figure 2). We did not see any association between estimated genetic ancestry and menarche in whites or African Americans [37]. The effect of estimated global ancestry on age at menarche is small, and it likely does not fully explain the differences observed among racial/ethnic groups. However, further study of the racial/ethnic group-specific factors that modulate the timing of puberty is another strategy that will likely inform further our understanding of the regulation of pubertal timing in the general population.

Summary

The timing of puberty varies greatly among individuals and much of this variation is due to inherited factors. However, the exact causes and mechanisms that underlie this variation remain largely unknown. There has been much progress in identifying genes underlying reproductive endocrine disorders such as KS and HH, but the genes and variants that influence the normal spectrum of pubertal timing are just beginning to emerge. It is clear that to understand the regulation of pubertal timing in the general population more fully, it will be necessary to look beyond the common variants that have been and will be identified through large-scale GWA studies. The next step will likely be new forms of GWA studies and large-scale sequencing efforts to look for rarer genetic variants than those captured by GWA arrays as well as investigation of other modes of inheritance such as copy number variants and epigenetics. It is likely that as the techniques used to investigate pubertal timing expand our understanding of the regulation of pubertal timing will expand as well.

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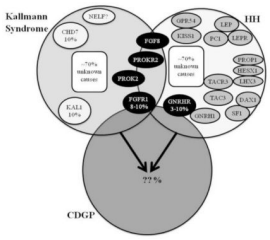

Figure 1. Genetic basis of delayed puberty

A paradigm for understanding the genetics of puberty is shown. Some genes underlying the pathogenesis of Kallmann Syndrome (KS) and hypogonadotropic hypogonadism (HH) have been identified and are depicted with each diagnosis; less is known about the genetic basis of Constitutional Delay of Growth and Puberty (CDGP). There is overlap between the three clinical entities as illustrated by the overlapping circles. There is also likely overlap in their genetic bases, as has been reported for *FGFR1* (in KS, HH, and CDGP), *GNRHR* (in HH and possibly CDGP), *PROK2* (in KS and HH), *PROKR2* (in KS and HH), *FGF8* (in KS and HH), and *CHD7* (in KS and HH). Thus far, mutations in only *GNRHR* and *FGFR1* have been found in cases of delayed puberty who are members of families with HH or KS but who themselves have no features of the more severe disorders [35,49,50]. Whether genetic variation in these genes plays a role in modulating pubertal timing in the general population (outside of families with HH or KS) is not clear [36,37] and has yet to be proven experimentally. In both KS and HH, approximately 70% of the genetic causes are still unknown. (Please see text for a more detailed discussion of these genes and their roles in these disorders.)

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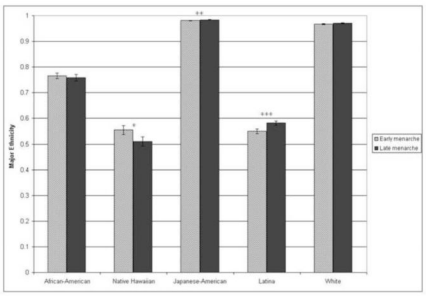

Figure 2. Genetic ancestry and age at menarche

Mean ancestry estimates for each self-reported racial/ethnic group separated by early and late menarche. The “major ethnicity” on the y-axis represents the estimated contribution of the ancestry that has the largest contribution to a given self-reported ethnic group. For African-Americans, major ethnicity is estimated West African ancestry; for Native Hawaiians, major ethnicity is estimated Native Hawaiian ancestry; for Japanese-Americans, major ethnicity is estimated East Asian ancestry; for Latinas, major ethnicity is estimated European ancestry; for whites, major ethnicity is estimated European ancestry. ***$p<0.01$, **$p<0.05$, *$p<0.1$. Figure reproduced with permission from Journal of Clinical Endocrinology and Metabolism 93: 4290–4298. Copyright 2008, The Endocrine Society.

Table 1

Quantitative Trait Loci (QTLs) associated with age at menarche (AAM) in linkage analyses

Compiled data from several studies indicating significant QTLs (with LOD scores) associated with age at menarche. Those results with evidence of statistically significant linkage are shown in bold; areas with only suggestive linkage are in normal text. In Rothenbuler *et al.* the analyses for AAM found only nominally significant QTLs; however, when AAM was adjusted for weight standard deviation score (weight SDS) at menarche, several significant QTLs were identified. The bottom row represents data from mice showing a significant linkage with timing of vaginal opening (VO), a marker of pubertal onset in mice, on the region of mouse chromosome 6 that correlates with human chromosome 12p11–12. Table modified with permission from Kaminski BA and Palmert MR. Human Puberty: Physiology, Progression, and Genetic Regulation of Variation in Onset. In: D Pfaff, A Arnold, A Etgen, S Fahrbach, and R Rubin, editors. Hormones, Brain, and Behavior (2nd ed). Elsevier Science (USA), San Diego, CA. Copyright Elsevier 2008.

	Human Chromosome							
Trait (Reference)	**1**	**4**	**6**	**8**	**12**	**16**	**18**	**22**
AAM (Guo et al. 2006)								22q11 (2.68) **22q13** (3.70)
AAM (Long et al. 2005)			6q25.3 (2.01)					
AAM (Rothenbuhler et al. 2006)								
AAM/weight SDS (Rothenbuhler et al. 2006)				8p12 (2.18)		**16q12** (3.12) **16q21** (3.33) 16q21 (2.46)		
AAM (Anderson et al. 2008)	1 (2.4), UK only	4 (2.0), UK only			12q (2.0)		18 (3.2), UK only	
Age at VO (Nathan et al. 2006)					**12p11- 12**			