Genetics of reproductive lifespan

Patricia Hartge

Five genome-wide association studies of the timing of menarche and menopause have now taken us beyond the range of candidate gene and linkage studies. The list of new genetic associations identified for these two traits should shed light on the mechanisms of ovarian aging, as well as breast cancer and other diseases associated with reproductive lifespan.

Menarche and menopause constitute fundamental biological events during a woman's life, and a complex set of environmental and genetic factors controls the time of their occurrence[1–6]. Although family and twin studies previously suggested that at least half of the variation in age at first and last menstruation is inherited, the genes contributing to these traits have not been identified. In this issue, five separate papers report genome-wide association studies (GWAS) for age at menarche and/or age at natural menopause[7–11]. The collective findings should open promising new avenues for research into the mechanisms underlying ovarian aging.

Insights into the genetic basis of the reproductive lifespan could have clinical value for understanding, preventing or treating disorders of puberty or menopause. In addition, a woman's age at menarche and her age at menopause relate to many aspects of human health (**Fig. 1**). For many of these long-term health effects, the association is unexplained. Thus, the genetic associations reported in the studies in this issue should provide insight not only into the timing of menarche and menopause but also may yield needed breakthroughs in understanding the genetic variation conferring risk of breast cancer, cardiovascular disease and other health events of later adulthood.

Within this set of papers, four GWA analyses establish that common genetic markers near a height-related gene, *LIN28B* (6q21), are related to menarche[7–10]. Less definitively, they also report a locus on 9q31.2 and several other loci also associated with age at menarche. In addition, two GWA analyses of age at menopause strongly point to a role for *BRSK1* (19q13.42) and *MCM8* (20p12.3). Less strongly, they also implicate *UIMC1* (5q35.2), *SYCP2L* (6p24.2) and a locus at 13q34 (refs. 7,11). Markedly, these five independent studies agree on the genetic loci identified to have stronger effects on these two traits. For the additional loci with suggestive evidence, further combined analyses should reveal which additional genes belong on the growing list of those that control these milestones of the reproductive lifespan.

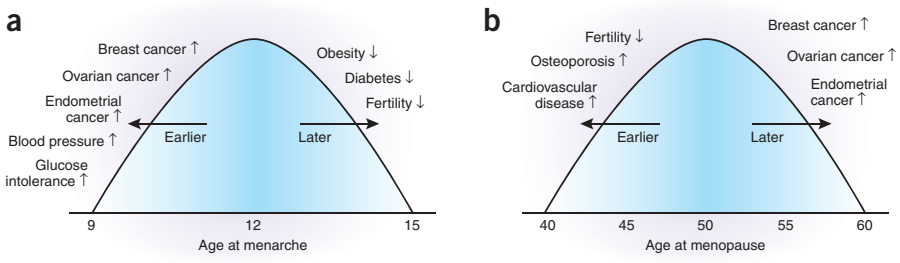

Figure 1 Potential health impacts of ovarian aging. (**a**,**b**) The timing of both age at menarche (**a**) and age at natural menopause (**b**) has a wide range of effects on human health. Shown are a range of conditions, in which age at menarche and age at natural menopause are known or suspected to either increase (↑) or reduce (↓) risks of these disorders.

When reproductive lifespan begins…

LIN28B stands out as a trigger for menarche because of its previous association to adult height. It is notable that it alone, of the many height-related genes, surfaced as a predictor of menarche. Height gain in childhood precedes menarche, which then slows growth, so early maturers are taller as girls but shorter as women. More investigations into *LIN28B* may help to disentangle height trajectory, weight gain, and the successive stages of puberty. For example, a longitudinal study of development recently examined height-related genes according to their separate effects on the main parameters of the infancy and puberty growth spurts[12]. Identification of menarche-associated genes should refine our understanding. Ong *et al.* also examine longitudinal measurements of development in girls and boys, suggesting several associations that require further replication[8].

Weight also relates to menarcheal age. Weight gain precedes menarche, so heavier girls mature earlier, and they continue to be heavier as women. Perry *et al.* and Sulem *et al.* each report that some genomic regions related to adult body mass also affect menarcheal age, even after adjustment for the effects of adult body mass[9,10]. Further studies should resolve the genes affecting childhood and adult weight, and their connections to menarche.

Weight and height, the main triggers of menarche, have strong genetic components, but they also are heavily determined by nutrition, which therefore is the key environmental influence on age at puberty[3]. Average menarcheal age responds very quickly to changed nutritional status, with long delays observed during famine. For example, it has been shown

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that in poorer nations, well-nourished girls may mature one year earlier than the average. Similarly, adopted girls from poorer nations tend toward the menarcheal age of their new peers. Steep downward trends in age at menarche have been documented over long periods (two or three years per century), with decelerating but continuing trends in the most recent decades in the United States[3]. Physical activity also affects menarche, with delays of one or two years for athletes who begin training as girls, and it may also contribute at the population level, not exclusively by effects on body mass.

These nongenetic effects surpass those seen for any single marker found in the new GWA studies. For example, among non-Hispanic white girls in the United States, 80% reach menarche between 11.3 and 13.8 years of age, so the two-month delay associated with a variant in *LIN28B* is small compared to the 30-month normal range[1]. Nonetheless, each delay from a known genetic variant may suggest a mechanism of action, in turn revealing more about the normal sequence of maturation and its response to nutritional status.

Research in chronic disease also stands to benefit from these discoveries. We have known for years that girls with delayed menarche show reduced risk of breast cancer decades later, but we still do not know why. Longer cumulative exposures to estrogen and progesterone, or specific hormonal exposures during a window of susceptibility, may lead to more proliferation of breast epithelium. This model may apply, but we need to find the specific hormone(s) and timing of the window. In recent studies, a five-year delay in menarche has been shown to correspond to a 7% reduction in risk of ductal carcinoma but a 35% reduction for lobular[13]. Sulem *et al.* report exploratory expression profiling for *LIN28B*, an approach to find tissue-specific and hormone-specific effects[4]. Similar questions in cardiovascular and other diseases can be probed with the newly discovered associations[11].

…And when it ends

Like menarche, menopause typically occurs during a fairly narrow window of age, with timing controlled approximately equally by nongenetic factors and genes. He *et al.* and Stolk *et al.* identify genomic regions that harbor two excellent candidate genes, *BRSK1* and *MCM*[7,11]. In addition, He *et al.*[7] implicate regions including *UIMC1* and *SYCP2L*, and Stolk *et al.*[11] point to a region on 13q34 that is an apparent gene desert. In developed nations today, menopause usually occurs between ages 45 and 55 years (median, 50–51). The genetic variants identified in these two studies were together estimated to produce a 5- to 12-month advance or delay. This suggests that further genetic associations remain to be discovered, and additional variants may be expected to emerge from analyses of combined and additional datasets.

These genetic associations may not offer direct clinical applications today, but they are a step towards understanding premature menopause, reduced fertility and other direct features of the reproductive lifespan. Further studies on sisters with very different menopause ages or women with extreme phenotypes (for either menarche or menopause) may reveal more about the effects of the newly identified loci and uncover additional ones. The associated genetic variants will also open the door to mechanistic studies of the effects of menopause on bone loss, cardiovascular disease and cancers of the breast, endometrium and ovary. Does a gene that influences menopause directly affect the risk of a menopause-related cancer? How are variants in *BRSK1* or *MCM8* related to breast cancer risk among women of the same age at menopause? As the biological effects of menopause-related variants begin to emerge from further studies in various model systems, these can be compared to breast carcinogenesis models. This burst of initial discovery of genes associated with age at menarche and at menopause builds on epidemiologic studies with detailed data from well-defined source populations. These and similar studies can now reexamine many established but unexplained associations between menstrual history and risk of adult diseases, important problems in need of new approaches.

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Diversifying microtubules in brain development

Andrew P Jackson

Tubulins are key structural components of all cells. A new study reveals roles in brain development for a specific β-tubulin isoform and highlights potential for functional diversity in the β-tubulin gene family.

Microtubules are important structural components of all cells, contributing to the cytoskeleton, cilia, flagella, axon fibers and mitotic spindles. As such, they are crucial for many cellular functions, including axon formation, determination of cell shape and motility, trafficking of intracellular components and mitosis. Microtubules are conceptually simple structures built from two basic building blocks, α- and β-tubulin, which form heterodimers and polymerize to form tubular structures. Mutations affecting such proteins would be expected to be poorly tolerated, particularly as these tubulins have maintained 75–85% sequence identity across most plants, animals and fungi[1]. On page 746 of this issue, Jamel Chelly and colleagues[2] report that *de novo* heterozygous mutations in *TUBB2B* (beta 2b tubulin) cause malformations of the brain, manifesting as asymmetrical polymicrogyria. This directly implicates microtubules in the etiology of polymicrogyria and shows the developmental requirements for one particular β-tubulin isoform from the repertoire of ten human β-tubulin genes.

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Tubulins and neurodevelopment

Asymmetric cell division of neuronal progenitors generates cortical neurons that then migrate along radial glial cells to their final destination at the surface of the cerebral cortex. Several 'neuronal migration disorders'